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CONTRIBUTION TO THE STUDY OF THE SYMPATHETIC NERVES OF THE APPENDIX. THE MUSCULONERVOUS COMPLEX OF THE SUBMUCOSA*

P. MASSON

(From the Department of Pathological Anatomy of the University of Montreal, Montreal, Canada)

Describing the lesions following acute appendicitis, pathologists speak of cicatricial scleroses of the submucosa which invade the circular muscle and dissociate its bundles more or less. Their illustrations show the muscle bundles separated from one another and turned from their normal course so that some of them seem to lose themselves in the fibrous connective tissue of the submucosa; the boundary between the submucosa and the circular muscle is no longer so clearly marked as in the normal intestine.

Beyond question, up to a certain point, postinflammatory sclerosis explains this partial dislocation of the muscularis and the musculoconnective tissue interpenetration; but, if this were the only cause, we should be obliged to admit that all appendices without exception have been diseased, even those of nurslings and of the new-born, for all of them present in different degrees the same ill-defined boundary between the circular muscle and the submucosa. From this observation what conclusion can be drawn other than that this lack of precision of the boundary does not result exclusively from sclerosis, but that it corresponds at least in part to a normal structure? This was the point of departure of the present study.

I first observed this condition in beginning my investigation of nerve proliferation in the appendicular mucosa and the origin of argentaffin cell tumors (carcinoids). While pursuing this work I

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acquired the idea, little by little, of a submucous muscular mechanism, then of a submucous musculonervous complex, present in all appendices. My brief description in 1924 and again in 1928 has attracted no attention. If I now return to the subject it is because this complex seems to me worthy of notice by its constancy and by its peculiarities, both in the normal and the pathological state.

As we shall see, marked variations in the musculonervous complex are habitually accompanied by obvious changes, always of the same order, in the other appendicular constituents, always involving the submucosa, often the mucosa and sometimes the muscular coat. From this observation arose the idea that these changes are not unconnected with those of the mechanism itself and that their study is capable of throwing light on its significance. I shall not, therefore, limit the description to the complex itself but, in connection with each example studied, I shall indicate the condition of the other appendicular structures.

I. Appendices of the New-Born

Normal Type: (Figs. 1 and 3.) In the first place we must describe this complex in the surely normal appendix, that of the new-born or of the nursling. At this age the appendicular mucosa is habitually poor in lymph nodules and rich in crypts of Lieberkühn. The muscularis mucosae forms an almost continuous layer beneath the tips of the crypts, interrupted only in the region of certain lymph nodules.

The submucosa is thin and already fibrous. Study of the bundles of circular muscle surrounding it shows that from time to time certain bundles change their course and pass obliquely into the fibrous connective tissue in which they seem to lose themselves. In the submucosa, centrally from these oblique muscle bundles, we find other, more slender bundles presenting at most eight to ten contractile fibers abreast, which seem to be isolated in the fibrous connective tissue. From the muscularis mucosae in the same sector, muscle bundles here and there detach themselves and bury themselves in the submucosa. Serial sections show that the muscle bundles of each group, the one issuing from the circular muscle, the other from the muscularis mucosae, converge and anastomose in the middle of the submucosa. Sometimes one or two muscle bundles cross this middle zone and join the two groups in one network.

I cannot say that this union is constant. The oblique course of the bundles makes it difficult to draw a conclusion. However, union is beyond question in certain instances where each group is conical in form. The base of one is continuous with the circular muscle, that of the other with the muscularis mucosae. Their apices are joined by one or two more or less oblique anastomotic bundles. In other specimens the ordinary location of the two groups in the same sector and the direction of their bundles toward each other indicates a certain correlation between them, even if they are not actually joined together. They form a whole which I propose to call the muscular mechanism or complex of the submucosa.

Each cross-section of an appendix shows elements belonging to several (two to four) of these mechanisms. We should note also these two points: (1) The arteries destined for the submucosa travel among the bundles emanating from the muscularis mucosae; and (2) Meissnerian nerves are always present between the bundles of a whole complex. As to their relations with the muscular mechanism, the evidence is not so good as that which we shall be able to offer later on.

II. Appendices of Children and Adolescents

Normal Type: Appendices removed from children and adolescents are much richer in lymph nodules, although their number and size vary greatly, not only from one specimen to another but also in different regions of the same specimen. Sometimes they are isolated, sometimes grouped in masses and more or less continuous at their borders. They may be small and lodged entirely in the mucosa, or they may encroach on the submucosa; and in this event, the most frequent, there is no muscularis mucosae beneath them.

Crypts of Lieberkühn are found only in the spaces between the lymph nodules at points where the nodules are not too closely approximated. It is only at these points, remaining glandular, that the muscularis mucosae persists. It is in these sectors provided with a muscularis mucosae, and consequently with crypts of Lieberkühn, that we find the anastomotic muscular mechanisms with the features already described. The submucosa is two or three times thicker than at an earlier age.

Pathological Types: In certain subjects in whom lymphatic tissue is developed to the utmost, such as status lymphaticus and certain

instances of chronic appendicitis, the lymph nodules are continuous or even heaped up in several layers, leaving space for only a small number of crypts beneath which no trace of a muscularis mucosae can be found. In these specimens a few bundles are seen to detach themselves from the circular muscle, but no contractile (smooth muscle) cell continues through the lymphoid tissue, encroaching on the submucosa. The internal half of the mechanism is wanting, as is the muscularis mucosae itself.

In children and adolescents, after one or more appendicular crises, quite frequently there is seen a reversal of the conditions just described, consisting in rarefaction of the lymph nodules and sclerous thickening of the submucosa. Often in this thickened submucosa the muscular mechanisms are more prominent than in the normal state. These variations indicate already on the one hand an inverse proportion between the richness of the mucosa in lymph nodules and in the number of the crypts; on the other hand a certain correlation between the gland content of the mucosa and the development of the muscular mechanisms of the submucosa. These contacts and relations are much more obvious in the adult, as we shall see.

III. Adult Appendices

All pathologists know how variable is the number of lymph nodules in the adult appendix. Study of a large number of specimens shows that on the average the number of these nodules is less than in children and that at times they are almost or completely absent. This lack of lymphoid nodules is habitually associated with former appendicular symptoms, acute crises or chronic appendicitis without acute inflammatory attacks, as if the spontaneous lymphoid involution had been hastened by these inflammations.

1. *Appendices with Numerous Lymph Nodules, Normal Type:* (Fig. 4.) The aspect of the mucosa is similar to that observed in the adolescent. The muscular mechanism presents no notable change. It is always found in the sectors provided with crypts.

In one specimen, exceptional it is true, I observed a mechanism more typical than usual (Fig. 2). Instead of showing along its whole length a plexiform structure, it was reduced to a perfectly straight and radial bundle visible in its entire length in one section, extending between the muscularis mucosae and the circular muscle,

to which latter it was attached by two or three oblique bundles. A branch of Meissner's plexus wound around it like a climbing plant. An artery of the mucosa traversed the muscularis mucosae in the immediate vicinity of its insertion.

2. *Appendices with Scanty Lymph Nodules, though Present in all Complete Cross-Sections. Passage from the Normal to the Pathological Type:* Sometimes the muscular mechanisms resemble those described above: they correspond to the normal type. Sometimes their bundles are obviously larger and more numerous. The mechanisms themselves are not increased in number. Their general form remains the same but they are seen more readily because of the greater number of their constituent bundles.

Along their whole length these mechanisms are mingled intimately with Meissnerian nerve filaments, distinctly larger and more numerous than in the normal state. These filaments, studded with tiny ganglia, form a plexus between the muscle bundles.

3. *Appendices with Very Scanty or Absent Lymph Nodules. Pathological Types:* (Figs. 5, 6 and 7.) This extreme diminution of lymph nodules is seen especially in the adult, seldom in the adolescent. Such an appendix almost invariably has a clinical history; repeated crises or a syndrome of chronic appendicitis. Its external appearance varies greatly. The length and caliber may be normal. It may be short, 3 to 4 cm., and correspondingly broad, 1 to 2 cm., or the tip may be swollen in the form of a pendulum. More rarely it is enlarged in all dimensions, 10 or even 15 cm. long, 1 to 2 cm. broad. Often it is buried in fibro-adipose peritoneum.

On examining sections with the naked eye, after fixation, the most striking features are the extreme narrowing of the lumen to such a degree that it seems to have been obliterated, and the thickening, often enormous, of the appendicular wall. The thickening involves the submucosa especially, but also in addition in extreme examples, the muscularis.

Appendices which combine these three fundamental features, narrowing of the lumen, extreme diminution or absence of the lymph nodules and thickening of the submucosa, present also more or less complex changes in their histological constituents. At first sight their situation, nature and extent seem to be capricious. Study of a large number of specimens has enabled me to establish a certain order among them. The most constant change affects the

muscles and nerves of the submucosa. This may be the only lesion but it is often accompanied by a curious alteration in the nerve plexus of the mucosa, to which may be added hypertrophy of the muscle coat and even of Auerbach's plexus. In this order, then, we shall study them: first the submucosa, followed by the mucosa and the muscularis.

Submucosa

The thickness of the submucosa, always excessive, varies from 0.25 to 0.5 cm. It is constantly fibrous, poor in fat cells but always of loose texture, especially in the middle. In this region there is often an imperfect cleavage into two concentric layers, the one fusing with the mucosa, the other with the circular muscle.

The muscular mechanisms and Meissner's plexus are prominent, obviously hypertrophied. The hypertrophy may affect only Meissner's plexus; its nerves are broad, elongated and tortuous, the ganglia larger, more numerous and richer in cells than in the normal state while the muscular mechanism, moderately but distinctly enlarged, contains only a few bundles. In the neighborhood of the circular muscle these bundles are thick; toward the muscularis mucosae they are slender and plexiform, always mingled with Meissnerian nerve filaments.

The Meissnerian hyperplasia, though present, may be masked more or less by hyperplasia of the muscular mechanisms, the contractile fibers striking the attention by their bright color (Fig. 8). The muscle bundles continuous with those of the circular muscle occupy the outer half of the submucosa. They ramify in different directions. Some of them converge toward the middle zone of the submucosa forming cones broader and better furnished with fibers than in the normal mechanisms; others run parallel with the axis of the appendix and seem to establish longitudinal anastomoses between the hyperplastic mechanisms from one segment of the appendix to another. Whatever direction they take the bundles are cylindrical. In the neighborhood of the circular muscle their fibers run parallel with one another. As they bury themselves in the submucosa the fibers become oblique, wavy, and they arrange themselves in the interior of the bundle in fascicles anastomosing with one another so that each bundle has a plexiform structure.

The nerves, hyperplastic and studded with tiny ganglia, ramify

among the muscle bundles, often run along with them and give off branches which encircle them or penetrate their interior to follow a course parallel to the fascicles.

The inner half of the submucosa presents many muscle fibers, sometimes grouped in bundles intimately anastomosing, sometimes interlaced in a close-meshed plexus. Anastomosing with those of the muscularis mucosae these fibers may group themselves in plexiform sheets that parallel the muscularis mucosae and reduplicate it externally. These fibers or these bundles converge toward the summits of the muscle cones emanating from the circular muscle and anastomose with them here and there.

The interstices of this robust muscle plexus are occupied by a very rich and delicate nervous plexus containing many ganglion cells, and by arteries destined for the mucosa (Fig. 15). The abundance of the nerves, and especially of the muscles, varies within wide limits. In certain specimens their mass may be estimated at one-half to two-thirds of the tissue present in the submucosa; that is to say, the total thickening of the submucosa is due in great part to their presence.

Such is the aspect of the musculonervous complex in most examples of lymphoid atrophy of the mucosa. However, I shall now describe the curious structure presented in some of my specimens by those muscle bundles, which issuing from the circular muscle assume a longitudinal direction (Figs. 16 and 17). These large bundles, round in cross-section and plexiform in structure, are not in direct contact with the connective tissue of the submucosa but are separated from it by a continuous sheath of varying thickness formed by a plexus of non-medullated nerve fibers. The nerve fibers are voluminous and appear edematous. The nerves sheathe the bundles only in their longitudinal ramifications; when the bundles take another direction the nerve sheath resolves itself into ordinary filaments. The nerve fibers are pressed closely together, anastomosing in a plexus of meshes elongated in the direction of the muscle bundles which they surround. Here and there the sheaths present small sympathetic ganglia with large cells. From time to time they are seen to give off small branches which penetrate the bundles and disappear between the muscle cells. This peculiar structure, though rare, shows very well the remarkable union of muscle and nerve in the complexes which are the subject of this study.

With these musculonervous hyperplasias are constantly associated important changes in the arteries. In the outer zone of the submucosa the lumina of the vessels are enlarged; their walls are thickened by hypertrophy of the muscle fibers as well as by interstitial sclerosis. Often there is notable thickening of the intima. The adventitia presents a nerve plexus of large tortuous fibers. The branches of the arteries directed toward the mucosa are more numerous than normal, tortuous, winding and mingled with muscle and nerve fibers. In short, all of the nervous and muscular elements of the submucosa undergo more or less hyperplasia, those of the arteries as well as those which belong to the musculonervous complexes.

Mucosa

Except for its poverty in lymph nodules the mucosa of the appendix may present nothing abnormal (Fig. 8). The crypts of Lieberkühn are numerous, straight and parallel as in the colon. Their tips may extend to the immediate vicinity of the muscularis mucosae. The mucosa does not contain an excessive number of nerves and the meshes of its stroma are filled with lymphocytes, plasma cells, and usually a few polymorphonuclear eosinophiles.

However, it may present more or less pronounced hyperplasia and even neuromas of the subglandular portion of the intramucous plexus. In this event the nerves always contain argentaffin cells, the form and origin of which I have described elsewhere. The meshes of the subglandular stroma, formed in large part by the hypertrophied nerves, are reduced to narrow clefts filled with lymphocytes. These cells are less numerous as the nerve hyperplasia is more pronounced. There results a relatively clear appearance of the deep region of the mucosa, which I have emphasized in former writings as a probable sign of hyperplasia of the subglandular plexus. Nerve lesions of this kind have no relation to the musculonervous hyperplasia of the submucosa. They may coexist, but the fact that the nerve lesions may be found without submucous hyperplasia shows that they do not depend upon it, in contrast to those which we are about to describe.

Here too the mucosa presents a stroma clear and poor in lymphocytes; but this appearance, instead of being restricted to the subglandular region and due to hypertrophy of its nerve fibers, extends

through the entire thickness of the mucosa. In addition, the stroma seems to be edematous and the enlarged meshes of its reticulum contain abundant fluid poor in free cells.

Often this edematous mucosa is thickened. The crypts are sometimes straight, sometimes sinuous and broadened. In this event their epithelium, as well as that of the appendicular lumen, presents some anomalies, larger, taller and broader cells clearly hypertrophied and hollowed by deeper calices than normal. Argentaffin cells are few (Figs. 12 and 14).

In studying this edematous mucosa as colored with the trichrome stain, an extreme richness of nerves is often observed. These nerves form a large part of the meshes of the reticulum but, in contrast to that which occurs in argentaffin cell nerve hyperplasia they are remarkably slender, containing one, two or at most three neuroglia tubes abreast. In certain specimens the nerves form multiple neuromas, which we shall now consider.

1. In the deeper half of the mucosa, there are diffuse neuromas which occupy large sectors. Their fibers are slender and closely approximated, leaving no room between them for a lymphatic space. Their course is capricious. Often they run more or less parallel and form whorls. These neuromas surround the lower half or lower third of the crypts. Their borders are ill-defined and continuous with the more loosely-meshed plexus of the general mucosa.

2. Circumscribed neuromas, always numerous and of small dimensions, which occupy the middle or the middle and upper region of the mucosa.

(*a*) The first group (Figs. 9, 10 and 11), consists of small round masses which after staining with the anilin blue trichrome appear as small, round blue spots situated between the tips of contiguous crypts, never between them and the muscularis mucosae. Their diameter averages one and one-half times that of the crypt. Their number may be enormous: I have counted forty in each cross-section of an appendix. They consist of a spherical mass of non-medullated fibers pressed closely together and anastomosing, united to the rest of the plexus of the mucosa by many fibers escaping from its surface. Each fiber of the neuroma is enclosed in a relatively thick collagen sheath, hyaline and fused together, giving the whole mass its blue tint with the trichrome stain. The collagen sheath is permeated by a network of argyrophil fibers (Laidlaw's technique), which are con-

tinuous with the reticulum of the adjacent mucosa. These neuromas never contain ganglion or argentaffin cells.

(*b*) The second and, in my experience, the most frequent form is situated between the crypts, stretching out parallel to them in the upper three-fourths of the mucosa (Figs. 12, 13, and 14). Some of these tumors are swollen in pendulum form, the pedicle occupying the level of the tips of the crypts while the swollen portion often reaches the superficial epithelium between two glandular orifices. These neuromas may be numerous, twenty-five to thirty per cross-section. Their structure is identical with that of the rounded neuromas just described. Over their entire surface they are continuous with the nerve plexus in the mucosa. In certain specimens their pedicle is in direct continuity with nerves emanating from the hyperplastic plexus of Meissner.

In short, whether diffuse or spherical, elongated or pendulum-shaped, these neuromas appear to be the result of localized hyperplasia of the nerve plexus of the mucosa, a hyperplasia characterized by lengthening of the fibers and the formation of spheres. The fibers remain very slender and are enclosed in relatively thick hyaline collagen sheaths. These neuromas are continuous with the hyperplastic plexus of Meissner of the submucosa. They never contain argentaffin or ganglion cells. Contrary to the argentaffin cell neuromas, which are situated exclusively between the muscularis mucosae and the tips of the crypts, they occupy the interglandular region of the mucosa and extend as far as the basal epithelium lining the lumen of the appendix.*

Muscularis and Auerbach's Plexus

Other changes, inconstant but, when they exist, always in combination affect: (1) The muscular coats, especially the circular muscle. The bundles are large and formed of hypertrophied fibers similar to those of the gravid uterus (Fig. 8). This hypertrophy involves even the smooth muscle of the meso-appendix. (2) Auerbach's

* I should say here that all attempts at silver impregnation of these hyperplastic nerves, those of the mucosa as well as those of the musculonervous complexes, have been futile. Critics will doubtless say, as has already been charged concerning the argentaffin cell neuromas, that I have seen nothing but neurinomatous proliferation. I must reply that, while positive impregnation of neurites has great value, a negative result proves nothing either way, considering the inconstancy of the method, especially for the myenteric sympathetic of the appendix.

plexus itself. The nerves are more voluminous and the ganglion cells are two or three times larger than normal: the filaments ramifying among the muscle bundles are prominent and studded with numerous ganglia.

When an appendix presents all of these hypertrophies and hyperplasias at once, muscular, nervous, vascular and even epithelial, its dimensions may become considerable; its length may attain 12 to 15 cm. and its external diameter 3 cm. Most frequently the length remains normal and the diameter only is increased.

In sections stained by ordinary methods, the most striking features are the size and abundance of the nerves and ganglion cells. In the submucosa the abundant elongated nuclei may be mistaken for nuclei of Remak, whereas a portion of them, usually the larger portion, belongs in reality to the muscle fibers, as shown by the trichrome stain.

Discussion

The lesions just described are of frequent occurrence. Not a week passes that my collection is not enriched with two or three specimens of musculonervous hyperplasia of the appendicular submucosa. Only the extreme examples with intramucous neuromas, hypertrophy of Auerbach's plexus and of the muscle coats and gigantism are relatively rare. Study of a large number of specimens shows that these giant appendices do not form an isolated group but that they are connected with the normal appendix by an infinite number of intermediate types. That these latter have not been described hitherto is doubtless due to the universal employment of techniques (hematoxylin and eosin, and Van Gieson), which do not reveal the muscles and nerves of the mucosa with sufficient clearness to strike the attention.

The literature contains a few observations, some of which should be revised in the light of the facts related here. Various authors have described ganglioneuromas, neurofibromatosis, Rankenneuromas, ganglioneuromas with or without gigantism of a given portion of the intestine. The site of the lesions is sometimes the small intestine (Pick, Baltisberger), sometimes the appendix (Heine, Oberndorfer, Schmincke, Schultz). The descriptions of these last four authors, especially that of Oberndorfer, suggest the thought that their specimens might represent musculonervous hyperplasia

carried to the extreme. At my request, Professor Oberndorfer had the kindness to send me some of his preparations. I recognized all of the features which he has described and illustrated so perfectly and my impression is that his giant appendix fits into the category of lesions described in this paper: thickening of the mucosa, lengthening of the crypts with hypertrophy of the cells, enormous diffuse intramucous neuroma, submucosa thickened and containing a gigantic nerve plexus and many muscle bundles, hypertrophy of Auerbach's plexus and thickening of the muscle coat.

At first sight, some details seem to differ from those that I have observed. Thus, in his Figures 37 and 38, Oberndorfer (1929) represents the "nerve" bundles surrrounded by ganglion cells. I question if these bundles are really nervous and not muscular, enclosed in a nerve sheath like those in my illustrations. I also question if the "syncytiale Bänder" of his Figure 39 do not relate to muscle rather than to nerve elements or, more exactly, neurinomatous elemants. Oberndorfer's stains, (hematoxylin and eosin, and iron hematoxylin) do not permit a definite answer to these questions.

Finally, Oberndorfer notes thickening of the nerves of the meso-appendix. I have observed nothing of this in my specimens, but none of them offers such extraordinary nerve hyperplasia as that of Oberndorfer. Is it not plausible that when pushed to the extreme the nerve hyperplasia may extend beyond the parietal plexus of the appendix and include the nerves of the meso-appendix itself?

In view of the participation of its various constituents in the enlargement of the appendix, Pick concludes that gigantism is "coordinated with" a fault in embryonic development, an excessive and tumoral growth of the local nervous system. For him, as for Oberndorfer, it is a congenital malformation. This view may be valid in certain instances. In my opinion it cannot be applied wholly to those which form the subject of this paper nor, perhaps, to Oberndorfer's specimen. While the influence of an excessive development of the sympathetic nerves on the growth of the other constituents of the appendix appears to me to be plausible enough, there is nothing in the instances cited in this paper to prove that the excessive growth has an embryonic origin. Its constant occurrence after frank crises, its primary situation in Meissner's plexus of the submucosa, its extension to a mucosa impoverished in lymph nodules

and enriched in crypts, then to the muscular coat and, finally, its frequency, seem rather to make of it an acquired lesion. This excessive growth is probably the result of appendicular inflammations, associated on the one hand with nerve regeneration following ulceration and on the other hand with a new growth of the mucous plexus more or less perfectly adapted to the new crypts that have replaced the involuted lymph nodules.

Other studies on the appendix have enabled me to verify the existence of nerve hyperplasias different from those described here, situated in the subglandular portion of the mucous plexus and there only. They are preceded by the migration of cells from the intestinal epithelium into the nerves. After penetrating the nerves these cells become loaded with silver-reducing granules and differentiate in various ways, some taking the form of ganglion cells, others of cells of Remak, while still others, cylindrical or spherical, elaborate fats which they eliminate directly into the nerves. Subsequently these nerves grow, lengthen and broaden to the point of forming neuromas; they are always situated beneath the tips of the crypts and are capable of pushing the muscularis mucosae into the submucosa (Fig. 18).

The epithelial covering of the mucosa often disappears and the lumen of the appendix becomes obliterated. The neuromas survive and even increase in obliterated appendices; they disappear if their argentaffin cells disappear. Their origin and their persistence are thus bound to the presence of these cells just as the existence of nerves of any kind is bound up with the presence of cells.

The impossibility of demonstrating neurites in these "neuromas" by the usual methods of silver impregnation has been urged as an objection to my views, and most writers have concluded that these growths are really neurinomas. In accepting this latter view we should be obliged to admit that the greater part of the nerves of the normal appendicular mucosa do not contain neurites either, because silver impregnations are negative for them also. Is this not placing too great reliance on the most capricious, the least reliable of techniques?

From another viewpoint the proliferation of Schwann cells in authentic neurinomas exhibits remarkable autonomy, but, in the argentaffin cell neuromas, proliferation and persistence of the nerve filaments is controlled by the presence of the cells emigrated from

the intestinal epithelium, just as the existence of nerves is bound up with the presence of the ganglion cells on which they depend. If, then, the hypothesis of the neuron is applicable to these neuromas it is certain that we must seek their trophic centers in the argentaffin cells and not elsewhere.

These observations have led me to the idea of a nervous system peculiar to the intestinal mucosa, of entodermic origin, a neurentoderm, characterized by the presence of ganglionic, neuroglial and secretory cells provided with silver-reducing granules, the neurites of which, indistinguishable by Cajal's methods, mingle with those of the sympathetic and form the plexus of the mucosa. This plexus then would contain two kinds of fibers, the one, centripetal, belonging to the neurentoderm, the other, centrifugal, starting from the sympathetic ganglia and arriving at the intestinal surface. Because of the organogenic analogies of this hypothetical system with the argentaffin cells and the placodic neuro-epithelium of the olfactory mucosa, I have thought that its function might be sensory rather than motor.

However, the conditions described in this paper have a totally different aspect. Meissner's plexus undergoes hyperplasia, either of its fibers only or of its ganglion cells also. There is a corresponding hyperplasia of the muscular mechanisms and of the arteries of the submucosa. At a further stage the hyperplasia involves certain nerve filaments of the mucosa, the centrifugal fibers just pictured which remain slender, lengthen and form superficial neuromas without argentaffin cells. At a still more advanced stage the muscle coat and Auerbach's plexus hypertrophy in their turn. These appendices have no tendency whatever to obliteration. If it occurs it is not the result of regression of the epithelium but of inflammatory ulceration. It is obvious that the site of these hyperplasias is a motor nervous system and the muscles which depend on it, above all the Meissnerian level of the intestinal sympathetic nervous system and the muscular mechanisms of the submucosa.

The neuro-argentaffin hyperplasias on the one hand and the sympathicomuscular hyperplasias on the other may exist in a pure state, which demonstrates their reciprocal independence and the independence of the two systems of nerves from which they arise. They are not incompatible. They may coexist in the same ap-

pendix, either in different regions or associated in the same sector, each preserving its own characteristics (Fig. 19).

Why not, then, admit the existence in the appendix of two groups of nerves, associated, mingled, indistinguishable in the normal state but recognizable under pathological conditions by their isolated or combined hyperplasias? The one is the argentaffin group, the other the myenteric group. Have these two groups distinct origins, as I am inclined to believe, or are they both of sympathetic origin, as stated by most neurologists? New researches will doubtless answer this question.

The significance of the musculonervous complex remains for me quite obscure. It is not easy to understand what mechanical rôle could be played by these contractile bundles buried in the submucosa. Nor is it easy to picture the organogenic processes of which they might be vestiges. They belong exclusively to the appendix. Does not their close association with motor nerves permit us to compare them with the neuromuscular nodes described by Keith in the muscularis of the colon, so little studied since, which play a part in intestinal motility? Still another problem.

Summary

The submucosa of the normal appendix contains muscle bundles, continuous on the one hand with those of the circular muscle and on the other hand with those of the muscularis mucosae. These two muscle groups often anastomose in the middle zone of the submucosa. They are in intimate relation with certain parts of Meissner's plexus. Muscle and nerve together form a complex which we may term the musculonervous complex of the appendicular submucosa.

Under influences that we cannot yet define, but connected no doubt with inflammatory crises, the muscle bundles and the nerves become more numerous, acquire more and more intimate relations, and by their accumulation contribute to the thickening of the submucosa. At the same time the arteries enlarge, their muscle coat hypertrophies and the arterial nerves become more prominent.

The mucosa presents certain changes which in the order of frequency are: decrease in number or complete absence of lymph

nodules, scarcity of lymphocytes in the stroma, and diffuse hyperplasia of its nerve plexus, to which may be added more localized hyperplasias in the form of ill-defined neuromas or circumscribed neuromas situated in the middle or upper part of the mucosa. In extreme examples there is in addition hypertrophy or hyperplasia of the muscle coat and of Auerbach's plexus.

To sum up, there is hyperplasia and hypertrophy either of the sympathetic nerves or of the appendicular muscles, or of both, in other words, of the motor apparatus of the appendix, together with atrophy of the lymphoid tissue. This series of lesions seems to begin by the formation of these musculonervous complexes.

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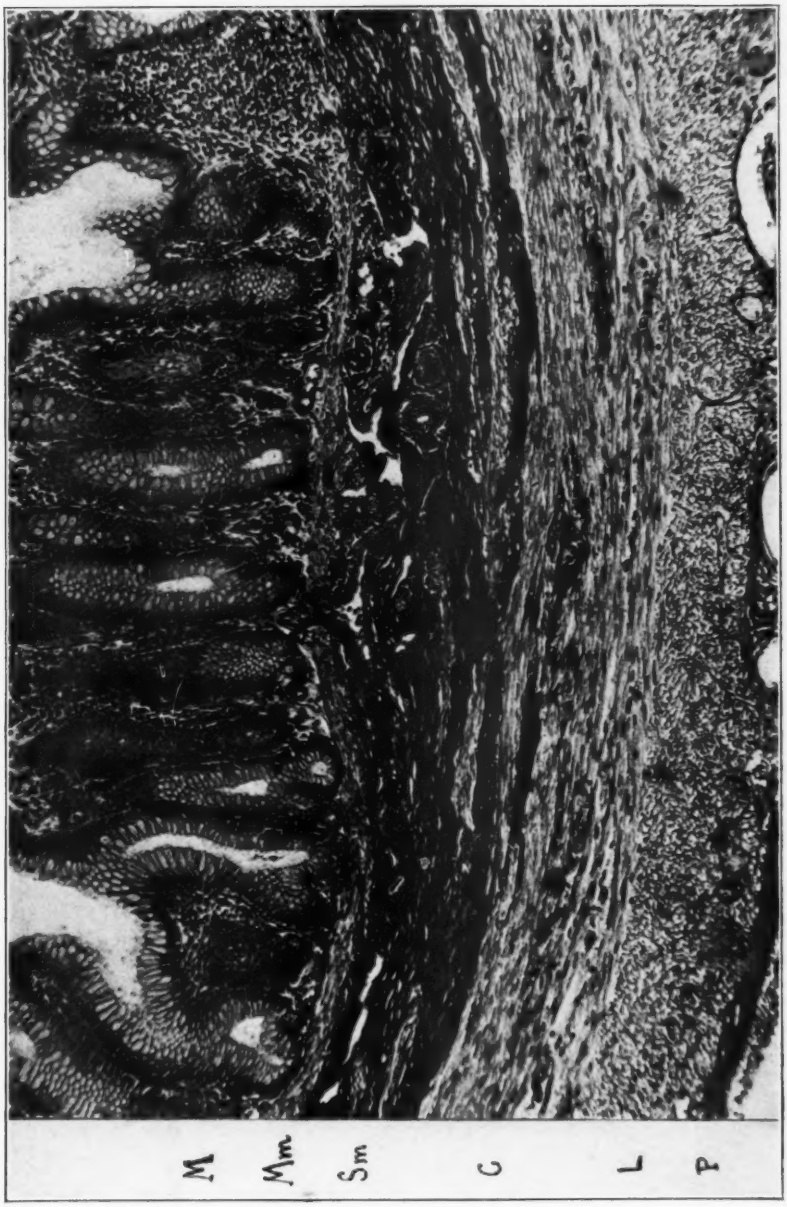
DESCRIPTION OF PLATES

PLATE 45

FIG. 1. Appendix removed from an infant of 4 months during an operation for congenital hernia. General view of a sector of the wall. Cross-section. (*m*) mucosa; (*mm*) muscularis mucosae perforated in the center by an arteriole destined for the mucosa and interrupted at the edge of the photograph by a primitive follicle; (*sm*) submucosa; (*c*) circular muscle; (*l*) longitudinal muscle; (*p*) peritoneum.

Note the muscle bundles (gray) anastomosing with those of the circular muscle, which invade the submucosa where they form a plexus continuous with slender muscle bundles emanating from the muscularis mucosae (cut nearly transversely) near the point of penetration of the artery. In the photograph the bundles appear as small gray circles near the broad lymph capillaries. This group of bundles forms a muscle complex. With the magnification employed, the nerves of Meissner's plexus ramifying in their meshes are not visible. This appendix is represented in Fig. 3 in its entirety.



1

Masson Musculonervous Complex of Appendix

PLATE 46

FIG. 2. Normal appendix from a patient 20 years of age. Above, the deep region of the mucosa rich in lymphoid tissue and bordered by the muscularis mucosae. Below, the circular muscle. Between the two, the submucosa traversed by a muscle bundle which unites the circular muscle and the muscularis mucosae. A Meissnerian nerve (black) accompanies it and winds around it. In this section it is visible only in the external portion of its course, but in serial sections it may be followed as far as the neighborhood of the muscularis mucosae where it ceases to be impregnated by the silver.

This musculonervous complex is typical in its simplicity but infrequent. A complete section of this appendix is represented in Fig. 4.

2

Masson Musculonervous Complex of Appendix

Plate 47

All the appendices represented in this Plate have been photographed with the same magnification in order to show the differences between normal appendices and those affected by hyperplasia of the musculonervous complex of the submucosa.

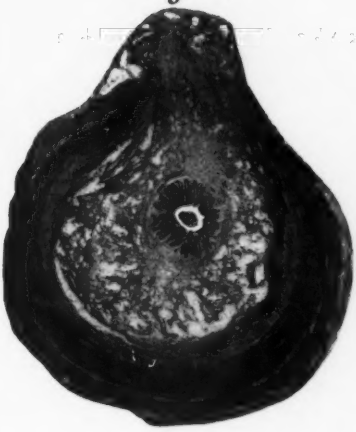
Fig. 3. Infant of 4 months (see Fig. 1). Broad lumen, mucosa rich in crypts and poor in lymphoid follicles, submucosa thin, muscle coat thin.

Fig. 4. Male, 20 years of age (see Fig. 2). Lumen relatively narrow, mucosa rich in lymphoid tissue, submucosa thicker, muscle coat scarcely thicker than in the infant.

Figs. 5, 6 and 7. Different degrees of hyperplasia of the musculonervous complex of the submucosa. Lumen narrow, mucosa rich in crypts, poor in follicles (6) or deprived of follicles (5 and 7). Muscularis mucosae continuous and thickened. Enormous thickening of the submucosa which splits incompletely into two concentric layers. Thickening of the muscle coat.

3

4



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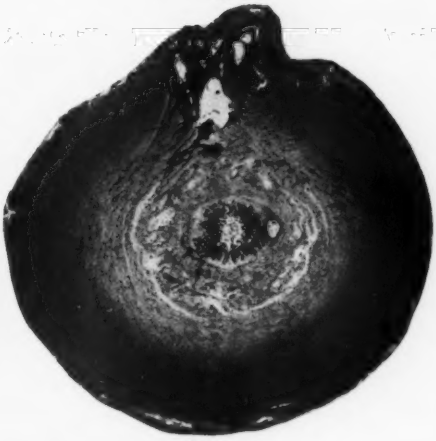

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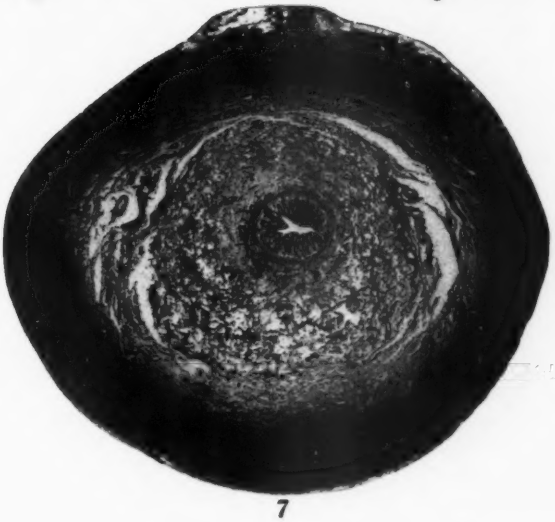


7

Masson

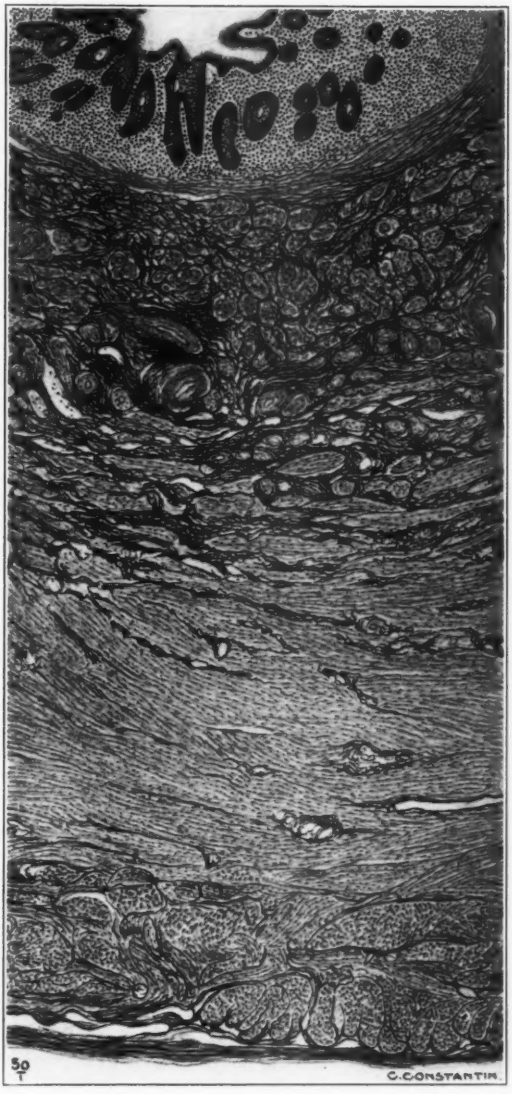
Musculonervous Complex of Appendix

Plate 48

Fig. 8. Appendix of Fig. 6 enlarged. (Obs. 126 M.) Trichrome.

Mucosa rich in crypts, the stroma clear, edematous, poor in lymphocytes. There are no intramucous neuromas in this specimen. Muscularis mucosae thickened. Submucosa enormous, crowded with muscle bundles in the interstices of which the connective tissue (black) is scanty. In the middle zone of this submucosa may be seen arterioles with hypertrophied walls.

Circular muscle greatly hypertrophied. No interstitial sclerosis. Its limits on the side of the submucosa are indistinct on account of the many muscle bundles that escape to form the hyperplastic muscle complex of the submucosa. Longitudinal muscle coat scarcely thickened. Peritoneum thin.

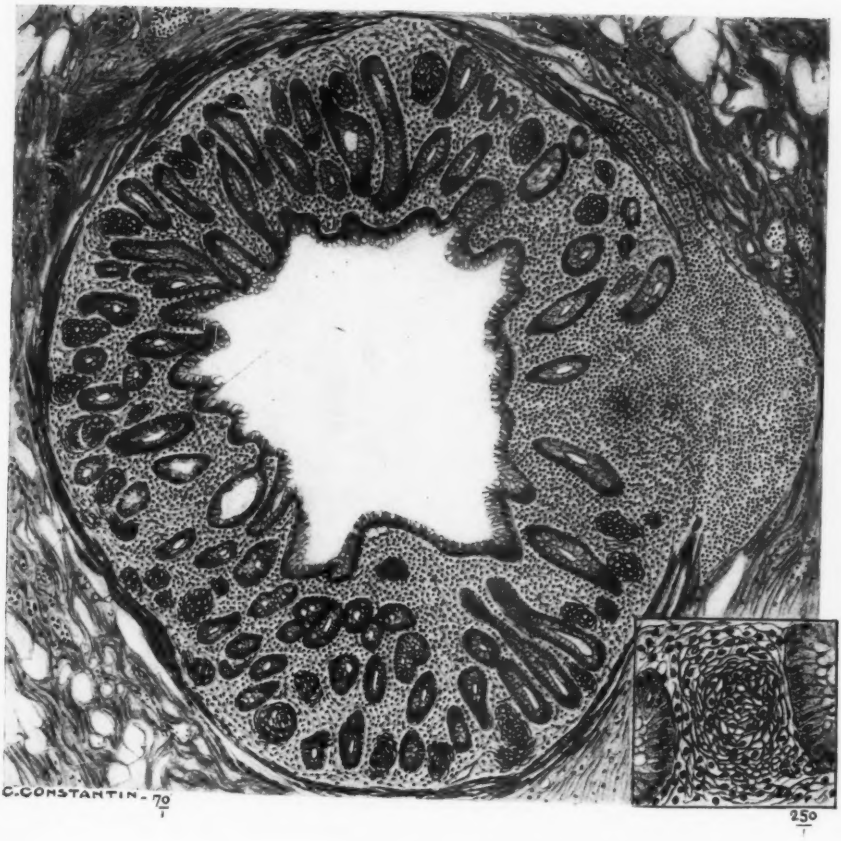


8

PLATE 49

FIG. 9. (Obs. 142 M.) Trichrome.

General view of a mucosa containing many spherical neuromas. Thirty may be counted in the figure. One of them is represented at a higher magnification in the corner of the figure.



9

Masson

Musculonervous Complex of Appendix

PLATE 50

FIGS. 10 and 11. (Obs. 142 M.) Laidlaw's silver technique.

The reticulin which surrounds the nerve fibers is continuous with that of the stroma of the mucosa: it leaves the fibers colorless while outlining the contours clearly.

10

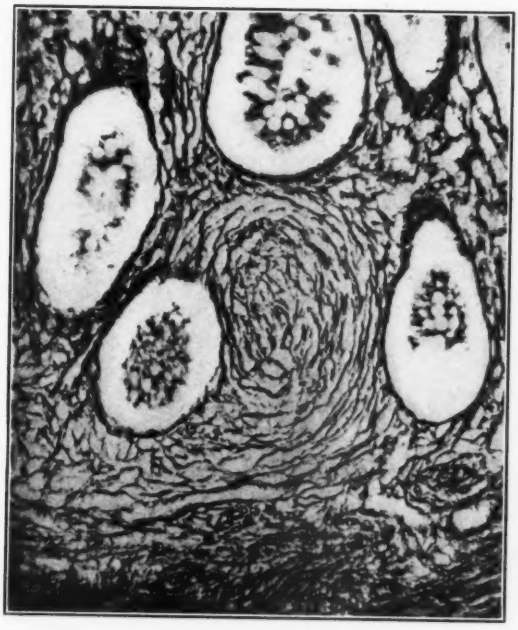


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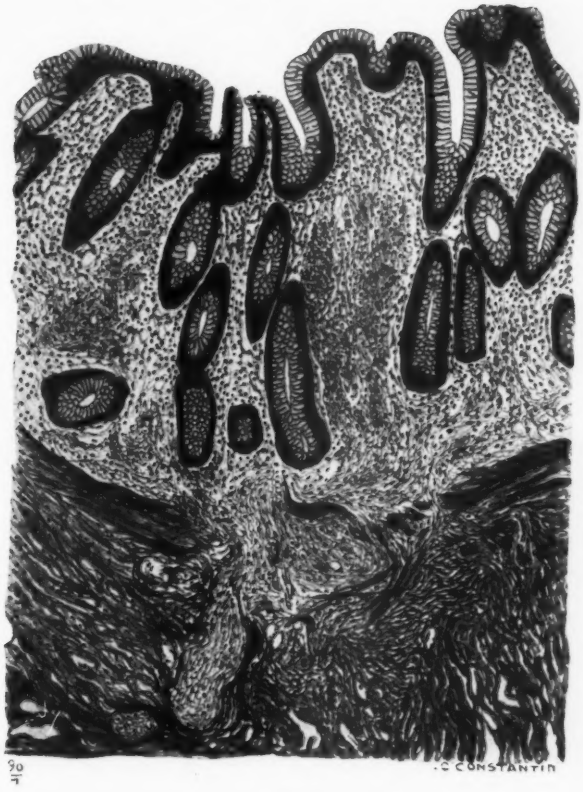
PLATE 51

FIG. 12. Same case as that of the general view, Fig. 7. (Obs. 68 M.) Trichrome.

Intramucous neuromas in pendulum form. Mucosa thickened, edematous. Crypts large and tortuous. Between them are two elongated neuromas connected by their bases with a diffuse neuroma which dissociates the muscularis mucosae and continues as a very broad Meissnerian nerve. The submucosa is traversed by innumerable nerve filaments invisible with this magnification.

FIG. 13. (Obs. 68 M.) Laidlaw's silver technique.

Two neuromas in pendulum form, their summits reaching the basal epithelium of the appendix. Here again only the contours of the nerve fibers are outlined by the reticulin which is continuous with that of the stroma.



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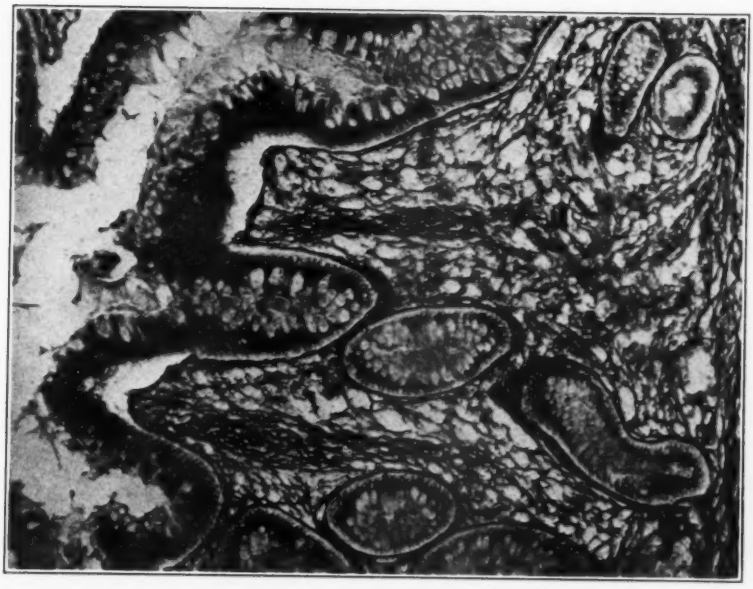


13

Masson Musculonervous Complex of Appendix

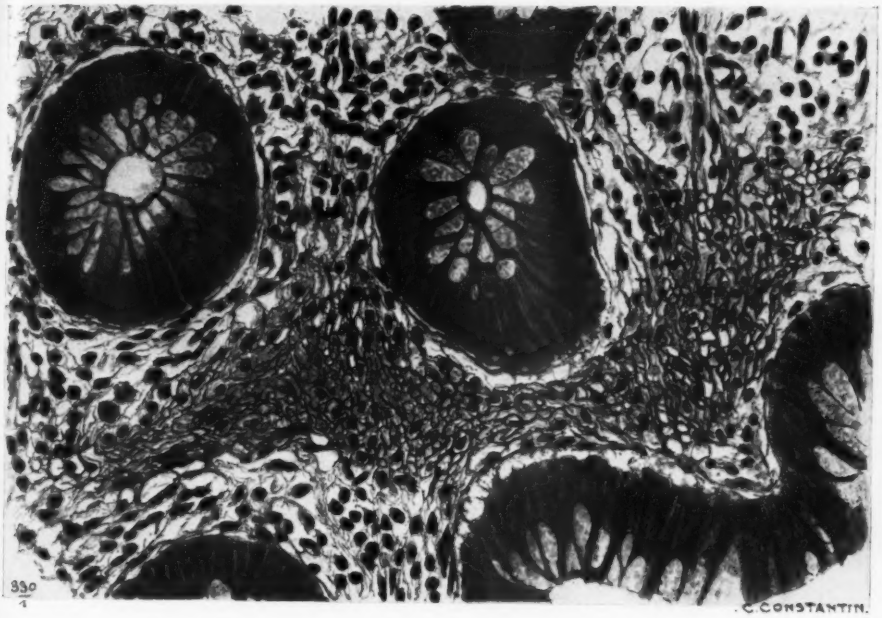
Plate 52

Fig. 14. (Obs. 68 M.) Trichrome.

Section of the mucosa near the surface and almost parallel to it. Note the considerable hypertrophy of the epithelial cells. Between them is a neuroma cut through the swollen portion. Note its irregular form, its compact texture, the thickness of the collagen sheath around each nerve fiber, the relative pallor of the nuclei of Remak and the continuity of these fibers with those which form an important part of the reticulated framework of the adjoining stroma.

Fig. 15. (Obs. 126 M.) Trichrome.

Hyperplasia of the musculonervous complex of the submucosa. Submucosa in the neighborhood of the muscularis mucosae. Confused interweaving of non-medullated nerve fibers recognizable by their spongy aspect, and muscle fibers oriented in every direction and sketching here and there small bundles. Fine nerve fibers are seen in the interstices between the muscle cells. A ganglion cell.



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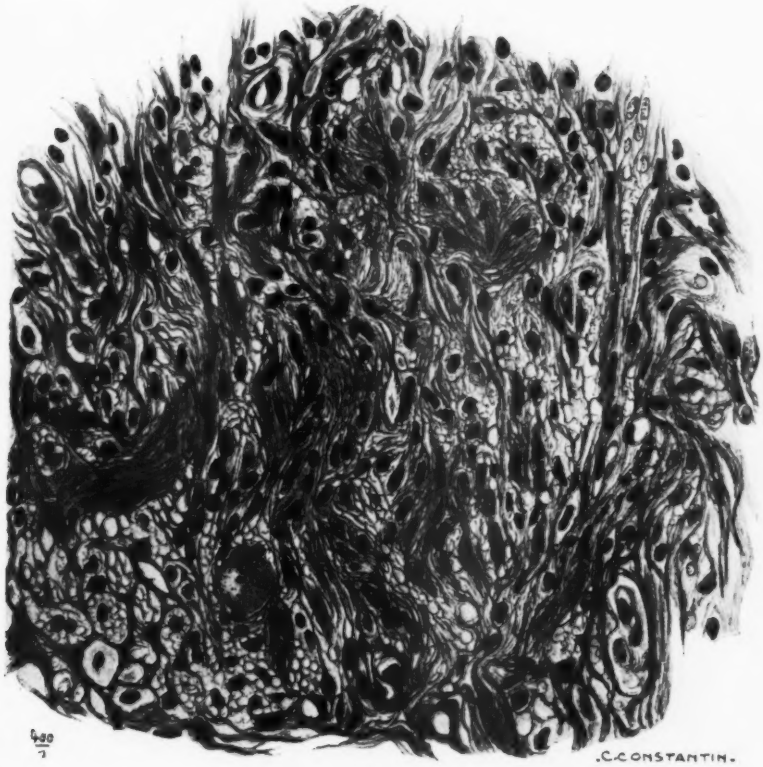


15

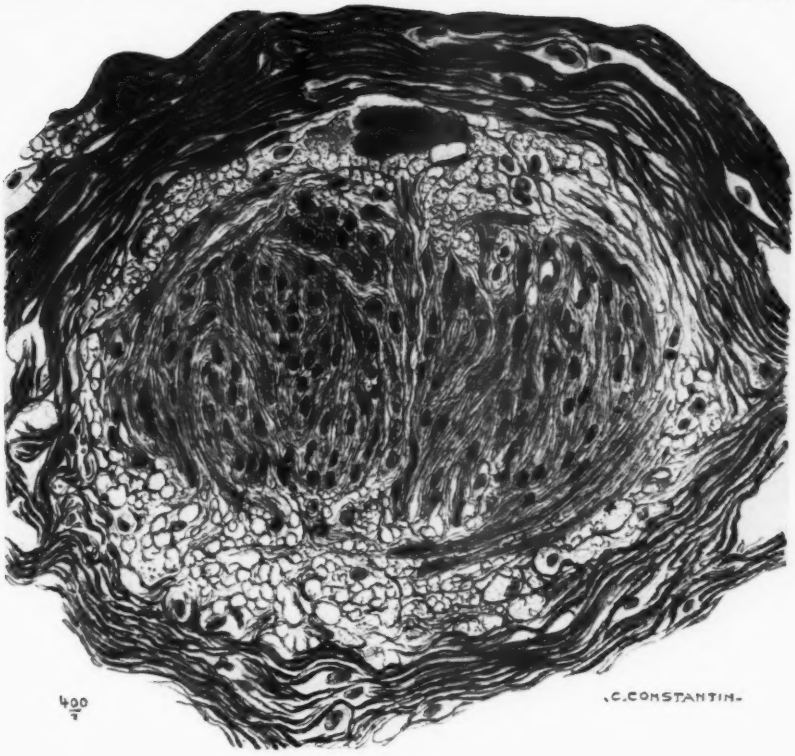
PLATE 53

FIG. 16. (Obs. 126 M.) Trichrome.

Submucosa in the vicinity of the circular muscle. A muscle bundle in a longitudinal direction in the neighborhood of a bifurcation. This bundle is surrounded by a continuous nerve sheath of longitudinal fibers. A large ganglion cell in the nerve sheath.

FIG. 17. (Obs. 126 M.) Trichrome.

The same musculonervous bundle after its bifurcation. Each branch has its own nerve sheath. A small sympathetic ganglion in the nerve sheath.



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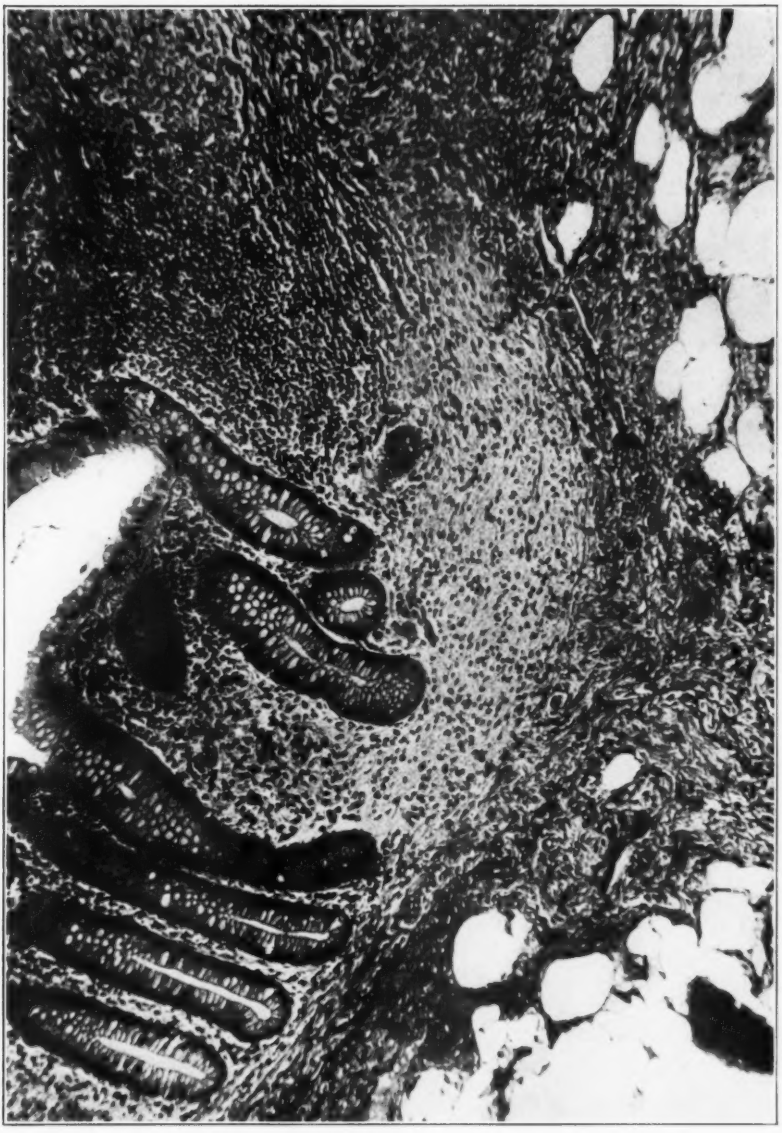
Masson Musculonervous Complex of Appendix

PLATE 54

FIG. 18. (Obs. 118 M.) Trichrome.

Intramucous argentaffin cell neuroma forming a clear mass between the tips of the crypts and the muscularis mucosae which is crowded into the submucosa.



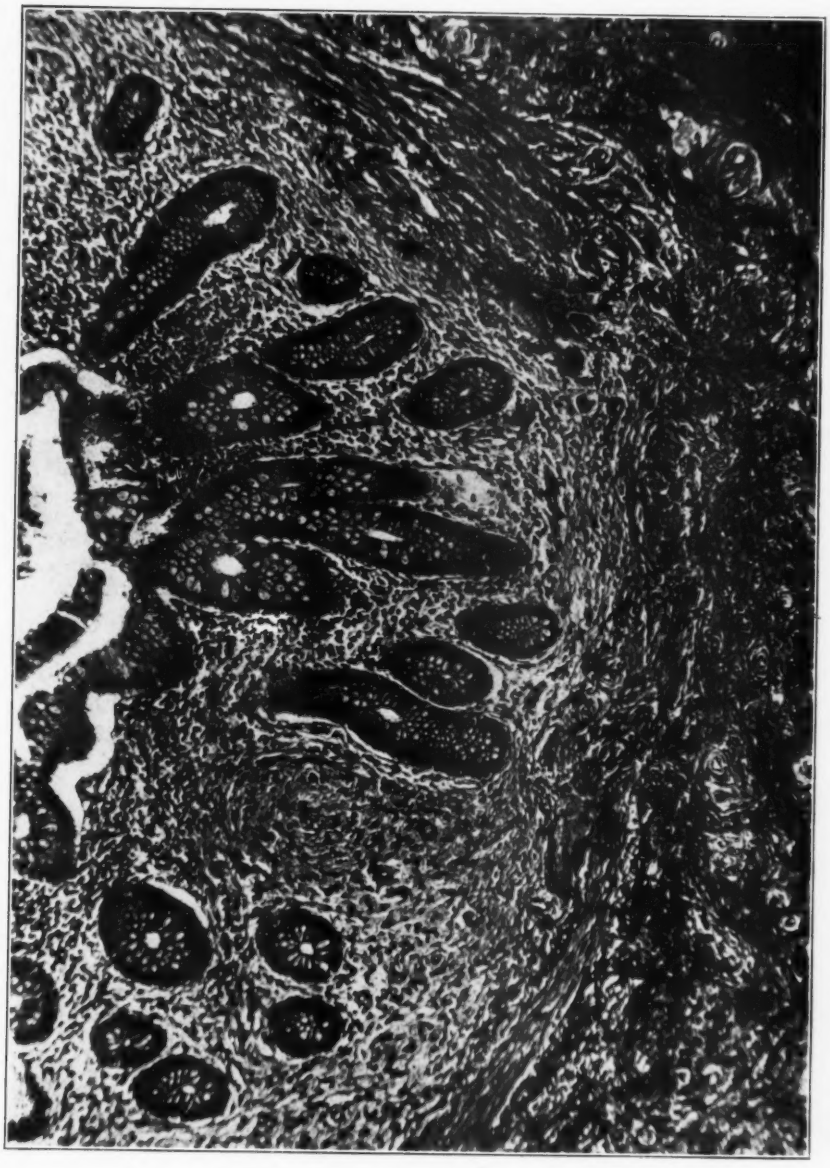
18

Masson Musculonervous Complex of Appendix

PLATE 55

FIG. 19. (Obs. 126 M.) Trichrome.

Association in the same region of the mucosa of a small, argentaffin cell neuroma (above), developed between the tips of the crypts and the bulging muscularis mucosae, and a pendulum-shaped neuroma connected with hyperplasia of the musculonervous complex of the submucosa (below).



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Masson Musculonervous Complex of Appendix

MULTIPLE INTRACRANIAL ANGIOMAS *

KIYOSHI HOSOI, M.D.
SENIOR EUGENE LITTAUER RESEARCH FELLOW IN PATHOLOGY, ALBANY MEDICAL COLLEGE
(From the Department of Pathology, Albany Medical College, and the Pathological Laboratory of the Albany Hospital, Albany, N. Y.)

INTRODUCTION

When one considers that multiple intracranial angiomas are very rare, the case reported here is most unique in that it was associated with the equally rare multiple intracranial meningiomas. Lindau [1] and more recently Dandy,[2] have made detailed studies of the venous abnormalities and angiomas of the brain, with excellent reviews of the literature on the subject. The general consensus is that these tumors are the result of a congenital anomaly of the vascular system of the brain.

REPORT OF CASE

Clinical History: M. H., white, female, married, 34 years of age, was admitted to the service of Dr. John A. Sampson, Albany Hospital, for cholecystectomy and freeing of numerous dense adhesions around the gall bladder.

As regards her past history the patient had had the usual diseases of childhood, appendectomy in 1914, pneumonia, and dilatation and curettage in 1919. She was pregnant three times, the last two being miscarriages which were followed by severe hemorrhages. Four years ago the patient had the usual picture of gall bladder disease with jaundice and clay-colored stools but refused operation. At that time she also complained of nocturnal (two or three times), and diurnal frequency of urination of moderate amounts accompanied by burning. Her urine, however, was negative. Blood sugar was 97 mg. per 100 cc., and basal metabolism minus 10 per cent. Other complaints were shortness of breath on exertion, palpitation of the heart and swelling of the ankles. Physical examination of the cardiovascular system at that time did not reveal anything remarkable. She had no cough, expectoration, night sweats or chest pains, but she gave a history of having had pulmonary tuberculosis several years before.

The patient had had no domestic difficulties, fits of anger or hysterical spells, but she had been having occasional dizzy spells and a feeling of pressure in the head. For the past three years she had been suffering from periods of depression lasting one to two days. During these periods she would cry a great deal. Because of these depressive states she was advised to enter the Poughkeepsie State Institution for observation but she refused to sign voluntary papers of commitment.

* Received for publication December 26, 1929.

As regards her present illness, the classical acute symptoms of gall bladder disease started four days before admission with colicky pains starting in the epigastrium, radiating along the right costal margin to the middle of the back, then to the right shoulder and arm, occasionally to the right thigh. This lasted one to three hours, leaving a residual skin tenderness in the right upper quadrant of the abdomen. Her urine became dark brown and the stools clay-colored. The jaundice had been present for the past six months. This attack was accompanied by chills and fever. The patient complained mostly of the vomiting, which was usually preceded by pain in the nape of the neck. This vomiting was food qualitative — strawberries, meats and tea. Fat, however, was tolerated well. No blood was seen in the vomitus which was occasionally green.

Physical examination showed a thin, under-nourished, slightly jaundiced female rambling from one point to another in giving her history, which was occasionally interrupted by threatened vomiting attacks. Clavicles were prominent. The expiratory phase at the apices was prolonged. Inspiratory râles were present posteriorly at the angles of the scapulae. Apices showed increased tactile fremitus posteriorly. Tenderness and spasm were found in the right upper quadrant of the abdomen. The knee jerks were equal. No clonus, Babinski, Kernig or Romberg signs.

Roentgen examination showed no gall stones. The duodenal cap was normal. The barium passed out of the stomach rapidly, massively filling the duodenum. Reverse peristalsis was noted in the duodenum. There was a slight six-hour gastric retention, most of the barium being in the terminal ileum, the ascending and first portions of the transverse colon.

The preoperative urinalysis was negative for sugar, albumin, acetone and diacetic acid. Kahn and Wassermann tests on the spinal fluid were negative.

Twenty-four hours after operation the patient suddenly developed an acute respiratory paralysis. She responded to artificial respiration but stopped breathing again after a few minutes. Further artificial respirations for at least two hours were of no avail.

Autopsy performed one hour after death gave the following unexpected findings: Multiple small angiomas of the cerebral cortex, multiple dural meningiomas, a pressure cone of the cerebellum and medulla, terminal bronchopneumonia, bilateral healed apical tuberculosis of the lungs, caseous tuberculosis of the right pulmonary lymph nodes, emphysema of the lungs, chronic adhesive pleuritis on the right side, atheroma of the aorta, mild nephrosclerosis, and a recent laparotomy wound for cholecystectomy.

Gross Findings in the Brain

The dura was stretched tense over the brain. The spinal fluid was clear. Through the external surface of the dura over the right frontal, parietal and temporal regions many opacities of various sizes could be seen, which later were found to be due to the presence of multiple meningiomas adherent to the inner dural surface. The

brain with dura weighed 1255 gm. Without further examination the brain and dura were suspended in 10 per cent neutral formalin. On frontal sectioning of the brain another large meningioma 4 by 3.5 by 4 cm. was found protruding into the right lateral ventricle. A detailed study of these multiple meningiomas will be reported in another paper.

When the dura mater was removed from the brain, after fixation, these meningioma nodules produced corresponding depression in the brain substance. The convolutions were markedly flattened and the sulci shallowed. The brain stem and the cerebellum showed a marked pressure cone.

The angiomatous nodules all occurred in the right frontal lobe, the smaller ones in the gray matter and the larger extending into the white substance. Located in the medial frontal gyrus 2.5 cm. from the medial fissure, there was a firm, circumscribed angioma 8 by 8 by 5 mm. Nearby, 5 mm. away were two other minute angiomas each about 1 mm. in diameter, lying wholly in the gray matter. In the marginal gyrus 3 cm. from the anterior frontal pole there were two more, measuring 7 by 10 by 4 mm., and 6 by 7 by 2 mm. respectively. In the same frontal section 1 cm. laterad from the median fissure, there were two others 5 by 7 by 2 mm., and 3 by 3 by 2 mm. in the cortex of the superior frontal gyrus. Further back in the marginal gyrus, 6 cm. from the anterior frontal pole and 5 mm. from the median fissure, there was still another angiomatous nodule 8 by 8 by 7 mm. The last figure in all the above dimensions represents the depth to which these tumor masses had penetrated the brain substance. These nodules produced on the external surface of the brain at the most only a very slight plateau-like elevation (Figs. 1, 2 and 3).

Microscopic Examination

Sections from the various parts of the brain were stained with hematoxylin and eosin, Van Gieson's picric-acid fuchsin, Mallory's phosphotungstic acid hematoxylin, Weigert's resorcin fuchsin, Verhoeff's elastic tissue stain, Foot and Mènard's method for reticulum,[3] and Penfield's combined method for oligodendroglia and microglia.[4]

In the various sections of the cerebral cortex all the cortical vessels stand out prominently, due to a marked hyaline and fibrotic thickening of the capillary wall (Fig. 4), and to the widely distended perivascular Virchow-Robin spaces. The nearer one gets to the angiomatous tumor areas the more prominent and the more numerous these vessels become. Numerous capillary angiomas of microscopic size are found scattered throughout the cortex of the frontal lobe. The smaller tumor areas consist of a complicated, branching, anastomosing network of capillary vessels, so strikingly shown in frozen sections stained by Penfield's method (Fig. 5). Very little collagen and no elastic fibrils are demonstrable in the younger angiomatous areas as shown by the Van Gieson, Weigert and Verhoeff stains. The older tumor nodules consist of closely packed hyaline masses in the center of each of which is a capillary lumen, either empty or containing red blood cells. Collagen is abundant and coarse elastic fibrils are demonstrable here and there in some of these older tumors. Reticulum is present only in the wall of the finer capillaries; none is found where there is increased collagen deposition.

In the white matter, just outside the distended perivascular spaces, there is a dense accumulation of numerous hyaline, spherical "amyloid" bodies. In those sections taken from the various parts of the brain, microglia and oligodendroglia are not increased in size or number.

Discussion

Compared with the other intracranial newgrowths, angiomas are not frequently observed. No mention of an angioma is made among 258 verified intracranial tumors by Tooth,[5] among 42 verified tumors by Heuer and Dandy,[6] 40 verified tumors by Greenfield,[7] or among 117 verified tumors by Purves-Stewart.[8] Cushing [9] found 8 or 0.9 per cent angiomas among 868 verified intracranial tumors. In a review of 100 verified intracranial growths, Dowman and Smith [10] found one angioma or 1 per cent. However, as mentioned previously, Lindau and Dandy have collected many isolated cases of angioma from the literature.

Autopsy revealed in the same patient here reported, multiple intracranial angiomas and multiple meningiomas. Unfortunately the spinal cord and meninges were not examined to find out if simi-

TABLE I.

TABLE I.

Number	Author	Sex	Age in years	Number of angiomas	Location of angiomas	Type of angiomas	Associated findings
1	Ohlmacher [13]	M	Adult	3	Callosal gyrus, optic thalamus, spinal cord.	Cavernous	Cranial meningioma, spinal osteoma.
2	Creite [16]	F	21	8	Both hemispheres, pons, cerebellum.	Cavernous	None
3	Finkelnburg [17]	M	14	2	Corpora quadrigemina, 4th ventricle extending into cord.	Cavernous	Cyst of cord, hydrocephalus.
4	Koch [18]	M	47	2	Cerebellum	Cyst with angioma in wall	Diabetes, lymphangioma of pancreas, cysts and fibroma of kidney, multiple adrenal rests in kidney, cavernoma of liver, capillary and cavernous angiomata of cord.
5	Huebschmann [19]	M	39	About 30	Both hemispheres	Cavernous	None
6	Friedrich and Stiehler [20]	M	41	2	Cerebellum, medulla.	Cyst with angioma in wall	Multiple cysts of pancreas, hydrocephalus.
7	Müller [21]	M	17	2	Caudate nuclei	Angioma arteriale racemosum	None
8	Malamud [22]	F	52	Numerous	Infundibulum, pallidum, pons-oblongata, both hemispheres.	Cavernous	None
9	Lindau [1]	M	32	Numerous	Cerebellum, medulla.	Cyst with angioma in wall, also capillary.	Hypernephroma, hydrocephalus.
10	Lindau [1]	..	..	3	Pons, cerebellum.	Cavernous	None
11	Fedoroff and Bogorad [23]	F	23	3	Frontal lobe, parietal lobe.	Cavernous	Cavernous angioma of spleen and kidney, breasts not developed, no menses.
12	Kufs [24]	M	81	Numerous	Both hemispheres, right pyramid, pons.	Cavernous	Multiple vascular nevi of skin, multiple cavernomas of liver, abnormal position of left adrenal.
13	Tannenberg [14]	F	34	Numerous	Cerebellum	Capillary	Angiomas of cord and adjacent spinal ganglion, angiomatosis of liver, cysts of pancreas and kidney, syringomyelia.
14	Here reported	F	34	Numerous	Frontal lobe	Capillary	Multiple cranial meningiomata

lar tumors were present there also. Wohlwill [11] and Schuback [12] separately reported the same case wherein a solitary angioma of the roof of the fourth ventricle was associated with an angiomatous tumor of the dorsal spinal cord. In the cases of Ohlmacher [13] and Tannenberg,[14] in addition to the multiple cranial angiomas, similar tumors were found in the spinal cord. Ohlmacher's case is of further interest in that the two cranial angiomas were also associated with a solitary cranial meningioma. Sands [15] reported a case of an angioma and a meningioma in one frontal lobe.

As seen in Table I, we have been able to find in the literature thirteen cases of multiple cranial angiomas. We consider Dandy's two cases (Nos. 6 and 7, reported by him as multiple angiomas) and Jaffé's case [25] as multiple telangiectases from their description and illustrations. Kalischer [26] described a case of multiple telangiectases of the left cerebral hemisphere, associated with a congenital telangiectasis of the left side of the face. Sachs [27] stresses this association and has found in the literature that the term angioma racemosum arteriale or venosum, had been applied to conditions which were not actually newgrowths. He suggested the name of intracranial telangiectasis for this condition. In our collected cases of multiple angiomata there were eight males to five females, with no sex mentioned in one case. The ages ranged from 14 to 81 years. No definite conclusions as regards the sex and age incidence can be drawn from such a small series. The multiplicity of these tumors varied from two to numerous. There appeared to be no site of predilection. Out of these fourteen collected cases, 8 or 57 per cent were associated with congenital anomalies or other types of newgrowths — multiple nevi of the skin, von Hippel's angioma of the retina, cavernomas of the liver, spleen and kidney, multiple cysts of the pancreas and kidney, one or more hypernephromas, one or more meningiomas, spinal osteoma, syringomyelia and hydrocephalus. Lindau has found that 20 per cent of the cases of von Hippel's disease have also an intracranial angioma. In my paper on multiple meningiomas [28] 45 per cent of the collected cases were associated with tumors of the acoustic nerve or generalized neurofibromatosis. This multiplicity in number and types of anomalies or newgrowths strongly suggests a congenital or dysontogenetic disturbance of the mesodermal germ layer.

Microscopically, most of these tumors have been cavernomas. A

few were of the capillary type. In others, the main tumor mass consisted of a cyst without epithelial lining, in the wall of which there was an angiomatous nodule.

Summary

1. A case of multiple intracranial angiomas associated with multiple intracranial meningiomas all on the right side, is reported with autopsy findings.

2. The patient presented no symptoms or signs of definite cerebral localization.

3. The literature on the subject is briefly reviewed.

Note: My thanks are due Dr. John A. Sampson for his kind permission to use the clinical history of this case, and Dr. Victor C. Jacobsen for his help and advice during the preparation of this paper.

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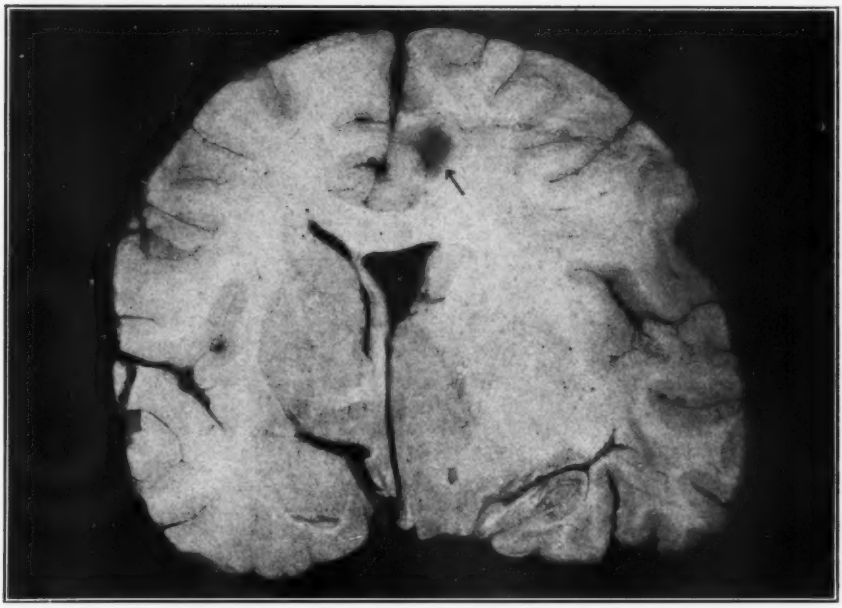
DESCRIPTION OF PLATES

PLATE 56

FIG. 1. Frontal section of the frontal lobe of the brain, looking from behind. Arrow points to a small angioma. The deep depression on the lateral surface is due to the presence of a meningioma on the corresponding inner surface of the dura.

FIG. 2. Two pieces from the mesial aspect and from the anterior pole of the right frontal lobe. The arrows point to four angiomas.

FIG. 3. Photomicrograph, Van Gieson stain. The large angioma produces very little elevation of the brain surface. Two other minute angiomas are present in the cortex (arrows). ×6.4.



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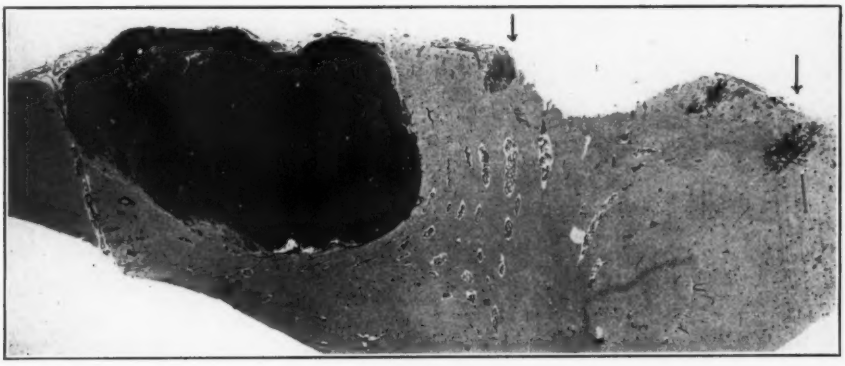


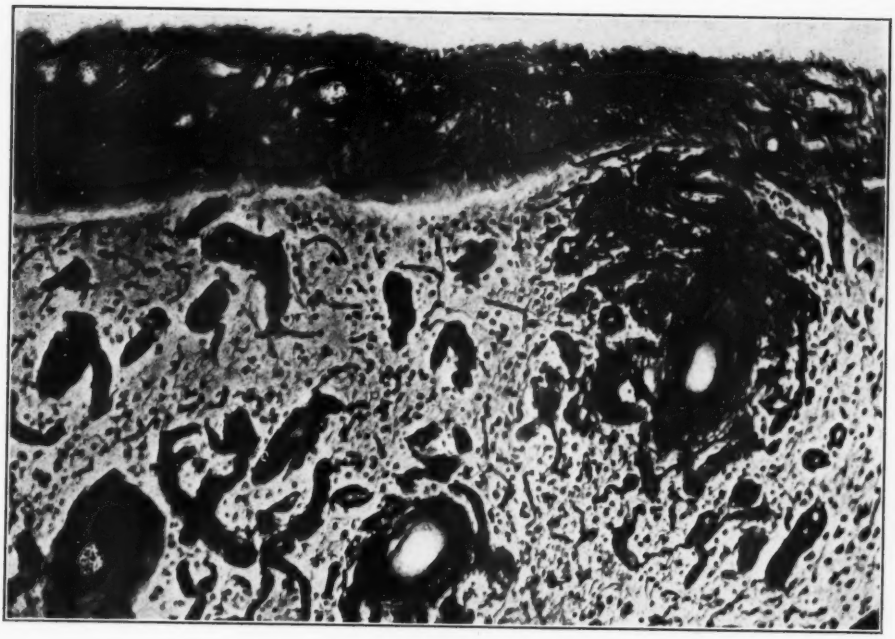
3

Hosoi Multiple Intracranial Angiomas

PLATE 57

FIG. 4. Photomicrograph, Penfield stain of a frozen section taken from the near vicinity of an angioma. Note the presence of numerous capillaries, their thickened walls and the highly branching forms. × 140.

FIG. 5. Photomicrograph, Penfield stain of a frozen section taken from the edge of an angioma to show the capillary nature of the tumor in the brain cortex. × 120.



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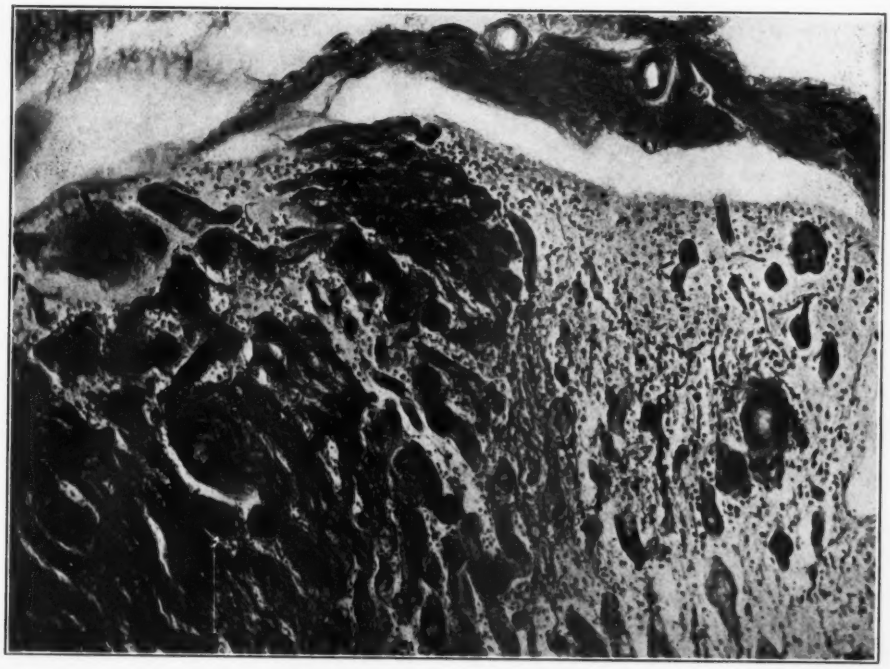

5

Hosoi Multiple Intracranial Angiomas

MENINGIOMAS *

WITH SPECIAL REFERENCE TO THE MULTIPLE INTRACRANIAL TYPE

KIYOSHI HOSOI, M.D.
SENIOR EUGENE LITTAUER RESEARCH FELLOW IN PATHOLOGY, ALBANY MEDICAL COLLEGE

(From the Department of Pathology, Albany Medical College, and the Pathological Laboratory of the Albany Hospital, Albany, N. Y.)

INTRODUCTION

Multiple meningiomas and solitary meningioma with hyperostosis cranei are of interest because of their infrequent occurrence. The histogenesis of these tumors is still much disputed. Additional cases in which detailed histological studies have been made may throw some light on the origin of these growths.

CASE REPORTS

CASE I

Clinical History: M. H., female, white, 34 years of age, was admitted in 1928 to the service of Dr. John A. Sampson, Albany Hospital, for cholecystectomy and freeing of numerous dense adhesions around the gall bladder.

As regards the pertinent facts of her past history she had had no fits of anger, hysterical spells or domestic difficulties. However, she had been suffering from periods of depression for the past three years, lasting one to two days. When depressed she cried a great deal. Because of these depressive states the patient was advised to enter a state institution for observation but she refused to sign voluntary papers of commitment. Also, she had been having occasional dizzy spells and the feeling of pressure in the head. The knee jerks were equal. No clonus was elicited and the Babinski, Kernig and Romberg signs were negative. Complement-fixation tests for syphilis on the spinal fluid were negative.

Twenty-four hours after operation an acute respiratory paralysis suddenly developed. She responded to artificial respiration and went on breathing naturally for a few minutes but stopped breathing again. As her cardiac function continued apparently undisturbed, further artificial respirations were heroically attempted for at least two hours but with no avail. This was a striking clinical demonstration of the independence of the cardiac and respiratory centers in the medulla.

Autopsy Findings: Autopsy performed one hour after death showed the following: Multiple dural meningiomas, multiple angiomas of the cerebral cortex, a pressure cone of the cerebellum and

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medulla, terminal bronchopneumonia, healed pulmonary tuberculosis of both apices, caseous tuberculosis of the right pulmonary lymph nodes, emphysema of the lungs, chronic adhesive pleuritis on the right side, atheroma of the aorta, mildly arteriosclerotic kidneys and recent laparotomy wound for cholecystectomy.

Head: The scalp was normal and stripped easily from the cranium. The skull cap and base were not remarkable. The middle ears were normal. The dura was tense over the brain. The spinal fluid was clear. Many opacities of various sizes could be seen through the external surface of the dura over the frontal, parietal and temporal regions. Brain with dura weighed 1255 gm. Brain and dura were suspended in 10 per cent neutral formalin.

On lifting away the dura from the brain cortex it was seen that the opacities mentioned previously were multiple, hard, sessile nodules and plaques attached to its inner surface, varying in size from 2 by 3 mm., to 13 by 18 by 10 mm. As shown in Fig. 1, these were present only in the right half of the dura. A total of thirty-eight nodules and plaques were counted. The largest nodule was attached to the inner surface of the dura in the region of the right Sylvian fissure. These dural nodules produced depressions on the corresponding surfaces of the brain. The convolutions appeared markedly flattened and the sulci shallowed. In the right hemisphere in the occipitoparietal lobes occupying the body and posterior cornu of the lateral ventricle there was found on frontal sectioning a firm, nodular growth 4 by 3.5 by 4 cm., of fibrous, gritty consistency (Fig. 2). The right chorioid plexus was strongly adherent to the inferolateral angle of the tumor. At first glance this tumor appeared to originate in the base of the brain, pushing into the ventricle and being easily enucleable. Microscopic sections and further study, however, showed that the growth was entirely covered by compressed brain tissue, which was of paper thinness just beneath the pia. The whole right striate body was pushed forward so that its frontal pole was 1.5 cm. anterior to that on the left side. The lateral ventricle on the left side was not dilated. The brain stem and cerebellum showed a marked pressure cone. The cerebral cortex of the right frontal lobe showed multiple small angiomas which are reported in another paper.

Microscopic Examination: Sections were stained with hematoxylin and eosin, Van Gieson's picric-acid fuchsin, Mallory's

phosphotungstic acid hematoxylin, Weigert's resorcin fuchsin, and Verhoeff's elastic tissue stain; in addition, Foot and Mènard's method for reticulum,[1] and Penfield's combined method for oligodendroglia and microglia [2] were used. As the brain had been fixed in neutral formalin the sections were first mordanted in potassium bichromate for several hours whenever necessary.

Sections from the ventricular tumor, stained with hematoxylin and eosin, show everywhere irregular interlacing bands of spindle cells with oval vesicular nucleus. Much collagen is present with a tendency toward whorl formation. In these collagenous areas there are calcific deposits, spiculated, sometimes irregularly oval, showing no concentric lamellations. Toward the periphery there are many masses of large polygonal endothelioid cells with large, oval to almost round vesicular nucleus. Many of these cells are arranged in whorl formation by themselves or around capillaries. Those cells forming larger whorls have become spindle-shaped. In still older whorls a few collagen fibrils are laid down between the cells. Much older whorls consist mainly of a lamellated fibrous tissue core. Some of these hyaline fibrous balls contain irregular calcium deposits in the center. Finally, psammoma bodies showing concentric calcification are most numerous in and around these cellular areas (Fig. 3). Along one edge, in close apposition to and adherent to the main tumor mass, the fibrotic but still vascular and tufty remains of the chorioid plexus can be distinguished. Most of the capillaries here are almost occluded, due to the thickened hyalinized fibrous wall. The remaining capillaries are widely dilated, appearing like venous sinuses. In the plexus there are a few calcified psammoma bodies and minute cellular clusters and whorls, which in serial sections show no connection with the main tumor (Fig. 4).

Sections taken from the dural tumors *en plaque* and of the nodular type all show a histological picture similar to the previous tumor — interlacing bundles of spindle-shaped cells with a tendency to cellular and fibrous whorl formation, collagen fibrils and psammoma bodies. The very small tumors *en plaque* contain only multiple minute cellular and fibrous whorls not yet calcified. These tumor masses are intimately connected with the dura. The dense collagenous fibers on the inner aspect of the dura are seen to fray out into the tumor tissue. A section through the region of the pacchionian granulations near the superior sagittal sinus shows many

cell clusters and whorls, indistinguishable histologically from those large whorls found in the various tumor masses.

In the section from the cerebral cortex, compressed by one of the larger dural tumor nodules, all the cortical vessels stand out prominently, due to a marked hyaline fibrotic thickening of the capillary wall. The perivascular Virchow-Robin spaces are widely distended.

In sections of the tumor masses stained with Van Gieson's picric-acid fuchsin, the pink-staining collagen fibrils are seen to permeate the tumor, occurring either as single strands or as dense thick masses and whorls. In other areas the broad bands of collagen produce a sort of honeycombed branching network, in the interstices of which one or more tumor cells lie. The collagen is present only around the blood vessels in the very cellular areas. In the smaller dural tumors collagen appears only as isolated, mostly short, thickened pink strands or nodes. The intimate connection between these tumors and the dura is even more noticeable in sections stained by this method. In some sections it appears as if the tumor cells have encircled each separate collagen component of the dura, producing numerous whorls with hyaline centers.

Weigert's resorcin fuchsin and Verhoeff's elastic tissue stains both show that elastic fibers are scarce in sections of the various tumor masses. None are found in the very cellular areas. In those areas where spindle cells predominate the elastic fibers appear as short thick strands or longer dark threads. In the collagenous areas these elastic fibrils run through the collagen bundles as long thick strands.

Mallory's phosphotungstic acid hematoxylin stain shows many fibroglia fibrils in the spindle cell areas. Reticulum, as stained by the Foot and Mènard method,[1] is absent in the very cellular areas of the large polyhedral cells; is abundant in the spindle-shaped cell regions (Fig. 5), and scarce in the very collagenous portions of the tumors.

In sections stained by Penfield's combined method [2] there is no demonstrable increase in size and number of the microglia and the oligodendroglia in the immediate vicinity of the large ventricular meningioma, nor in the cortex depressed by the numerous dural growths. However, a reactive increase in neuroglia fibrils is present in the brain tissue surrounding the ventricular tumor.

CASE 2

Clinical History: F. G., laborer, white, 45 years of age, was admitted in 1929 to the service of Dr. George S. Amsden for convulsions. He had had these epileptiform seizures for the past nineteen years. Since onset they had been more or less typically the same. First he moaned, then the right side of his face pulled up, his head turned to the right and his right arm began to jerk. He lost consciousness, frothed at the mouth, bit his tongue and was incontinent of urine and feces during an attack. When he came out of an attack he usually appeared perfectly normal. For many years these attacks had been occurring about once every two months. Soon they began to occur every day, and for the last two or three days he had had one attack every twenty minutes.

The physical examination showed a well developed and nourished man lying in bed and having an occasional convulsion. The order of events during one of these convulsions was: twitching of both sides of the face, mouth pulled over to the right, head and eyes pulled over far to the right, and then the right arm began to jerk clonically. The whole thing was over in about one to two minutes. During the attack the pupils did not react, the teeth clamped down and the sphincters relaxed.

There was a complete smoothing out of the lines on the right side of the face. The lips could not be drawn up. The forehead wrinkled equally well on both sides. Extra-ocular movements were normal. Fundi had been consistently negative. Tongue protruded with marked deviation to the right. Reflexes were diminished throughout but were apparently equal. No muscle weakness was elicited. There were varicose veins with an old varicose ulcer on the left leg.

The first and last 5 cc. tubes of the spinal fluid were perfectly clear but the middle tube showed definite xanthochromia. The initial pressure was 350 mm. water; bilateral jugular compression gave a prompt rise to 700 mm. and back to 300; right jugular compression gave a prompt rise to 350 mm. and back to 300; left jugular compression gave a prompt rise to 350 mm. and back to 300. After 5 cc. of the spinal fluid were removed, the pressure fell to 220 mm.; after 10 cc. removal, 190 mm.; after 15 cc. removal, 150 mm.; after 20 cc. removal, 120 mm.; and after 25 cc. removal, 100 mm. Cell count gave 7 cells per cmm. with a differential of 90 per cent lymphocytes. Pandy, Takata-Ara, Kahn and Wassermann tests of the spinal fluid were all negative.

During his seven days stay in the hospital the patient continued to have convulsions in spite of medication. He had as many as 100 convulsions during the course of twenty-four hours. At night he might have 50 convulsions. He seemed not to become exhausted, the convulsions being very light in character. He became gradually worse and his breathing labored. The left lung showed beginning hypostasis. Temperature rose to 108 , his pulse to 167, whereas his respirations which were 55 the day before fell to 48 about forty-five minutes before death.

Autopsy Findings: Autopsy performed one and one-fourth hours later is essentially not remarkable, excepting in the calvarium and the brain. In the left superior frontoparietal region near the midline the dura is strongly adherent to the internal surface of the skull cap over an area about 4.3 cm. in diameter. The inner table is invaded by a nodular tumor 8.7 by 6.4 by 4.8 cm., producing a hyperostosis

cranei. Here the calvarium is 20 mm. thick as compared with the 6 mm. of the opposite side. The external table is but very slightly elevated. The tumor apparently started near the midline compressing the brain caudad and laterad (Fig. 6). It extends 2 cm. from the frontal lobe anteriorly to the level of the Rolandic fissure posteriorly. There are numerous pacchionian granulations on each side of the falx cerebri in the vicinity of the growth. The largest of these measures 5 by 5 by 2.5 mm., being about 1 cm. away from the posterior pole of the growth, and having grossly the same appearance as the large tumor. Sulci and convolutions of the cortex do not appear shallowed or flattened. There is no cerebellar pressure cone. The cut surface of the growth after fixation is very fibrous, gritty and pearly gray. The edge of the tumor is sharply demarcated. Except for some filmy strands it can be easily shelled out. The left lenticulostriate body is not involved. The lateral ventricles are not very much compressed nor dilated, the anterior horn on the same side as the tumor being somewhat larger. Posteriorly the tumor penetrates the gray matter of the precentral gyrus over an area 2 mm. in diameter and 17 mm. from the median fissure, being adherent to the overlying pia-arachnoid.

Microscopic Examination: All the different staining methods mentioned under Case 1 were again employed here. The microscopic pictures after the various staining reactions are identical with those of Case 1. In Fig. 7, the invasion of the bone by the tumor cells is clearly shown.

Sections of the pacchionian granulations show many cellular nests and whorls. The chorioid plexuses contain many psammoma bodies and cell nests.

In the sections from the compressed brain the perivascular spaces of Virchow-Robin are widely distended. Numerous minute, spherical, partially calcified "amyloid" bodies are present here and there in the cortex; many are present in the endothelial lining cells of the cortical capillaries.

Discussion

Meningiomas may occur as a diffuse process, or may be single or multiple. The very rare diffuse form of meningioma or meningiomatosis has been reported under a variety of diagnoses by Bassoe and Shields,[3] Markus,[4] Greenfield,[5] Pirie,[6] Cassirer and Lewy,[7]

Moorhead and Wigham,[8] Fried,[9] Connor and Cushing,[10] and Casper.[11] Also, meningiomas may be histologically malignant. Craig [12] found eleven cases among fifty-six cases of intracranial meningiomas. Bailey [13] reported two cases of meningioma of the fibrosarcomatous type. Towne's [14] second case showed a meningioma of the falx cerebri with invasion of the inferior longitudinal sinus, extension into the straight, superior longitudinal, right and left lateral sinuses, jugular and innominate veins and superior vena cava.

Numerous instances of solitary meningiomas with or without cranial hyperostosis have already been reported by Cushing [15, 16, 17, 18] and his associates,[19, 20] Tooth,[21] Greenfield,[5] Alurralde and Sepich,[22] Holmes and Sargent,[23] Cordes,[24] and others. This hyperostosis cranei (hemicraniosis of the French) has been interpreted as being due to an osteoblastic invasion of the skull by the tumor (Penfield,[25] Phemister,[26] Sosman and Putnam,[27] and others), or as resulting from a defensive reaction of the bone to the progressing dilatation of the blood vessels (Kolodny [28]). In a study of ten cases of meningioma with cranial changes, Kolodny found that proliferation of bone precedes the infiltration of the skull by tumor cells. Spiller [29] also believes that the enlargement of the bone may come first. Wishart's case [30] is uniquely interesting in that there were two hyperostoses cranei, one of which had become perforated by the invading tumor. Also, in the cases of Mix [31] and of Dumas and Dechaume,[32] the dural growth penetrated the skull out into the scalp. The growth in Alurralde and Sepich's case was strongly adherent to the base of the skull in the right middle fossa. In Daspit's second case,[33] the dural meningioma perforated the temporal and sphenoid bones and extended down the neck and into the right sphenoid and posterior ethmoid sinuses. That all tumors perforating the vertex of the skull may not be due to a meningioma is shown by Daspit's first case of a perforating gliosarcoma. Cushing found that the bony thickening of the cranial vault is more apt to be much more pronounced in meningiomas *en plaque* than in the more massive type with a relatively small area of meningeal attachment. He has found them palpable externally, or demonstrable by X-ray in at least 25 per cent of the meningiomas. Furthermore, tumors parasagittal in origin and those arising from the temporofrontal meninges, adjacent to the Sylvian cleft, seem to be accompanied by hyperostosis cranei more often than those in other situations.

As seen in Table I, we have been able to find in the literature only twenty-two cases of multiple cranial meningiomas, including the one here reported. Globus [49] before the New York Neurological Society in 1928 mentioned that there was only one instance of multiple meningiomas out of a personal experience of 120 to 130 tumors but

TABLE I

Number	Author	Age in years	Sex	Number of primary meningeal tumors	Associated findings
1	Wishart [30]	21	M	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
2	Langdon [34]	32	F	Numerous	Unilateral acoustic tumor
3	Henneberg and Koch [35]	26	M	Numerous	Bilateral acoustic tumor
4	Schmidt [36]	77	M	2 tumors	None
5	Schmidt [36]	88	..	2 tumors	None
6	Fraenkel and Hunt [37]	42	F	Over 100 tumors	Bilateral acoustic tumors
7	Westphal [38]	26	F	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
8	Verocay [39]	31	M	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
9	Henschen [40]	25	M	Numerous	None
10	Leischner [41]	40	M	Numerous	Unilateral acoustic tumor
11	Heuer and Dandy [42]	Adult	M	2 tumors	None
12	Greenfield [5]	31	M	3 tumors	None
13	Symonds [43]	27	M	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
14	Krivy [44]	Old	F	3 tumors	None
15	Firket [45]	27	F	10 tumors	Bilateral acoustic tumors and one spinal meningioma
16	Casper [11]	Old	F	Numerous	None
17	Casper [11]	52	F	Numerous	None
18	Casper [11]	72	M	Numerous	None
19	Savy *et al.*[46]	39	F	2 tumors	None
20	Régniér *et al.*[47]	36	M	2 tumors	Bilateral acoustic tumors and multiple neurofibromatosis
21	Flick [48]	54	F	Numerous	None
22	Here reported	30	F	38 tumors	Multiple angiomata

he did not state whether the multiple condition was intracranial, intraspinal, or both. In the collected series there were eleven males to ten females with no sex data in one case — apparently no predilection for either sex. There is a wide variation in the age incidence as the youngest was 21 and the oldest, 88 years of age. There were

no other cranial findings in eleven cases; two had an associated unilateral tumor of the acoustic nerve, eight had in addition bilateral tumors of the acoustic nerve; and four of these last eight cases also showed multiple neurofibromatosis of the von Recklinghausen type of the cranial and peripheral nerves. Casper's third case is particularly interesting in that the two primary meningeal tumors were associated with a diffuse meningiomatosis of the pia-arachnoid and an endothelioma of the duodenum. In no case was the multiple nature of the meningiomas suspected before death.

Other interesting cases of multiple cranial and spinal tumors, though not strictly germane to this study, may be mentioned. Biggs' case [50] showed a bilateral tumor of the acoustic nerves and only one tumor of the falx cerebri. In a case reported by Schultze,[51] in addition to the cranial meningeal tumor there were multiple tumor nodules of the spinal pia, all histologically similar. In Funkenstein's case,[52] there were a psammoma and an osteopsammoma of the spinal dura associated with bilateral tumors of the cerebellopontine angle and multiple neurofibromatosis.

The frequent occurrence of multiple cranial meningiomas with bilateral acoustic nerve tumors and multiple neurofibromatosis has been regarded as being more than fortuitous by Verocay,[39] Cushing,[53] Firket,[45] and Régniér and his associates.[47] Both Verocay and Cushing interpret this in the light of some anomaly of development of the nervous system, whereas Régniér and his associates state that they have been able to find all transitions between the meningeal tumors and the tumors of the nerves. From Table I, it is seen that eleven, or 50 per cent of the cases were not associated with other types of tumor formation. This would suggest that the association of meningeal tumors and multiple neurofibromatosis is not an *a priori* relationship but an expression of the predisposition or susceptibility of the individual through hereditary and dysontogenetic influences.

It is to be noted here that solid cell clusters with a tendency to irregular massing of nuclei or formations of small whorls have been frequently noted in the arachnoid by Schmidt,[36] Le Gros Clark,[54] Weed,[55] and Winkelman and Wilson.[56] They occur at all ages from infancy on, but are an almost constant finding in the later decades of life. Weed found these cell clusters undergoing hyaline changes and calcification. Schmidt in 1910 first suggested that the so-called

dural endothelioma does not arise from the dural cellular elements but is of arachnoidal origin, either from the pacchionian granulations or from these cell clusters. Later, Weed, Winkelman and Wilson also pointed out the possible relationship of these cell nests to true meningiomas. Indeed, these cell whorls and clusters may be called miniature meningiomas as they correspond histologically to the fully developed meningeal tumor.

But what is the parent cell of this meningioma group of tumors? Their histogenesis is still a mooted question. Cushing suggested the name "meningioma" in view of the fact that its origin is still a disputed point and that the name is non-committal as regards its genesis from a particular type cell. Mallory [57] pointed out its fibroblastic nature by finding that elastic fibrils are elaborated by these tumor cells. Crowe and Jones [58] and Van Wagenen [59] confirmed Mallory's findings. However, Bailey [14] warns us that though in rare instances the cells of a meningioma may form fibroglia, collagen and elastin, this does not prove they are not endothelial cells. Maximow [60] watched in tissue cultures of the leptomeninges endothelial cells from the severed ends of small arteries growing out, forming side processes and losing their differences from fibroblasts. Kredel [61] noted that in young tissue cultures of meningiomas the typical cells seemed to be a mononuclear-macrophage series rather than fibroblasts, whereas in older cultures the cells appeared gradually to assume a form more closely resembling that of fibroblasts. More recently, Buckley and Eisenhardt [62] from tissue culture studies stated that the meningioma tumor cells which grew out in a reticular pattern are mesodermal, non-phagocytic cells. They state that these growing tumor cells did not appear to be of the fibroblastic type. On the other hand, Mallory and Parker [63] from histological study conclude that reticulum is collagen in separated form rendered prominent by the silver stain, that all collagen is produced by fibroblasts, that there are no reticular cells other than fibroblasts and that endothelial cells do not produce an intercellular substance. Yet Foot [64] has found much reticulum in a malignant endothelioma originating in the reticulo-endothelium of lymphoid tissue. To quote from him, "the morphological differences between vascular and reticulo-endothelium may, after all, be merely an evidence of a difference in the physiology of the same cell due to varying reactions to varying surroundings." Indeed, Piney [65] and more recently

Bailey, Cushing and Eisenhardt [19] believe that neoplastic endothelial cells may differentiate and form strands of reticulin so characteristic of these growths. In other words, a meningioma may belong to the reticulo-endothelioma group of tumors. We find that the tumor cells in both of our cases elaborate reticulum, fibroglia, collagen and elastic fibrils, all derivatives of mesodermal cells. Bailey, Cushing and Eisenhardt state that meningoblasts are capable of differentiation into angioblasts, fibroblasts, and possibly other types of cells. At any rate, tissue cultures and histological studies seem to indicate that the type cell of the meningioma is not fully differentiated, having endothelial and fibroblastic developmental tendencies which seems to depend on the stage of the differentiation, the younger, more cellular parts having endothelial characteristics and the older parts showing fibroblastic qualities.

It may not be amiss to review here briefly the embryology of the meninges. According to Wislocki,[66] the meninges in mammals arise as a differentiation of the middle germ layer about the neural tube.

The primitive mesenchyme condenses into two laminae, the outer of which becomes the dura, and the inner the leptomeninges. This inner lamina itself divides partially by a condensation of the mesenchyme, giving rise to the pia and arachnoid which remain connected with each other by a porous mesenchymal stroma. The subdural and subarachnoidal spaces are both lined by pavement-like mesothelial cells derived from the middle germ layer. Key and Retzius (1875), cited by Wislocki,[66] demonstrated by the silver impregnation method that the subdural space is lined by a continuous layer of mesothelial cells. The chorioid plexus arises from the membranous portion of the roof of the forebrain and hindbrain as a series of buds and folds, consisting of a richly vascularized connective tissue core derived from the periaxial mesenchyme, and a covering of epithelial cells, which represents a modified part of the ependymal lining of the ventricle. As regards the pacchionian granulations, Luschka (1855), cited by Wislocki,[66] first distinguished their origin from the arachnoid and named them "arachnoidal villi."

According to Bailey and Miller [67] the formation of blood vessels in all the higher vertebrates, including mammals, begins in the area opaca of the blastoderm. In this area the blood islands arise, being composed of rounded cells which have developed from the branched mesodermal (mesenchymal) cells. The superficial cells of an island

become the endothelium of the primitive blood cells. These blood spaces join one another and thus form a network of channels which soon ramify throughout the entire embryo.

Thus, as seen from the embryology of the meninges and of the vascular system, we are concerned strictly with the mesoderm in regard to the origin of the tumors in our cases; the multiplicity of these dural and angiomatous newgrowths in our first case would indicate a disturbance of the mesodermal germ layer, probably congenital.

We believe that the large ventricular tumor in our first case arose from the mesodermal elements of the chorioid plexus, an unusual origin for a meningioma. In support of this we find that: (*a*) the chorioid plexus is strongly adherent to the tumor mass; (*b*) this plexus contains numerous psammoma bodies and, what is more important, cell nests or whorls which by serial sections are found to have no connection with the tumor itself and which histologically are indistinguishable from the cellular areas of the tumor; (*c*) the tumor is surrounded on all sides by brain tissue, being wholly located in the lateral ventricle.

One would expect from the large size of the tumors in both of our cases, producing much pressure atrophy of the adjacent brain tissue, that there would be some reaction on the part of the interstitial tissue of the brain. However, microglia and oligodendroglia are not significantly increased or decreased. There is no demonstrable swelling of the oligodendroglia. Neuronophagia is absent. Only a moderate reactive gliosis is present in the immediate neighborhood of the ventricular tumor. All this bespeaks an extremely slow tumor growth in the two cases. In Case 2, it is definitely known that the onset of symptoms began nineteen years before death. Furthermore, this extreme slow growth is indicated by the presence of numerous psammoma bodies and abundant collagen fibrils, with very few cellular areas in these tumors.

Summary

1. Two cases of cranial meningioma are here presented: the first, one of multiple dural meningiomas associated with multiple angiomas of the cerebral cortex; and the other, a solitary meningioma with hyperostosis cranei.

2. The tumor cells of the meningioma are mesodermal in origin. They elaborate reticulum, fibroglia, collagen and elastic fibrils. The multiplicity of the intracranial meningiomas and the angiomas in Case 1 connotes a marked disturbance of the mesodermal germ layer.

3. Clinically and histologically, the meningiomas in these two cases indicate a long drawn-out course. Considering the large size attained by these growths it is remarkable that a brain tumor was not suspected. The first patient was thought to be a mental case due to her frequent depressive states associated with fits of crying. The second patient, who was under the constant care of a neurologist, was being treated for idiopathic epilepsy.

4. The brain tissue, immediately surrounding the meningiomas and the angiomas and also far removed from these growths, shows no reactive increase in microglia or oligodendroglia, although in the adjacent cerebral cortex of both cases, so-called "amyloid" bodies are very abundant. A reactive gliosis is present in the immediate neighborhood of the ventricular tumor.

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DESCRIPTION OF PLATES

PLATE 58

FIG. 1. Dural cap, inner view, showing the multiple meningiomas in nodular and plaque formation.

1

Hosoi

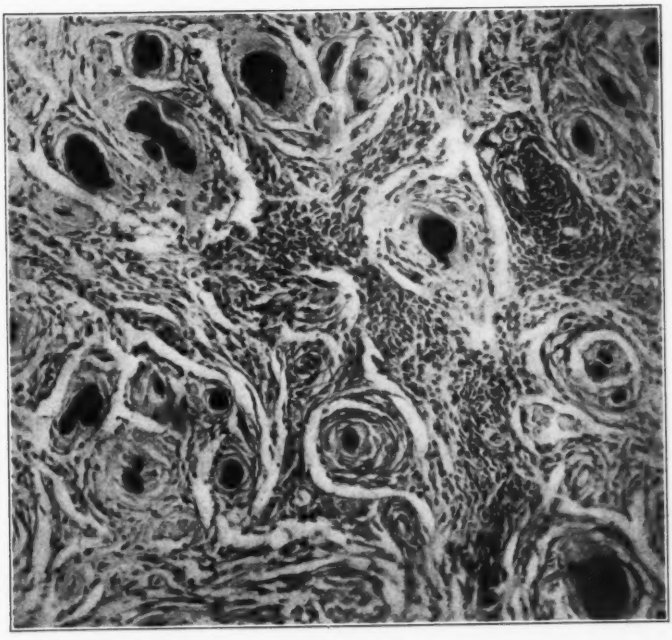
Meningiomas

PLATE 59

FIG. 2. Large meningioma filling the right lateral ventricle and apparently arising from the chorioid plexus.

FIG. 3. Photomicrograph of a section from the lateral ventricle meningioma. Note the whorl formation and the many psammoma bodies. × 126.

2



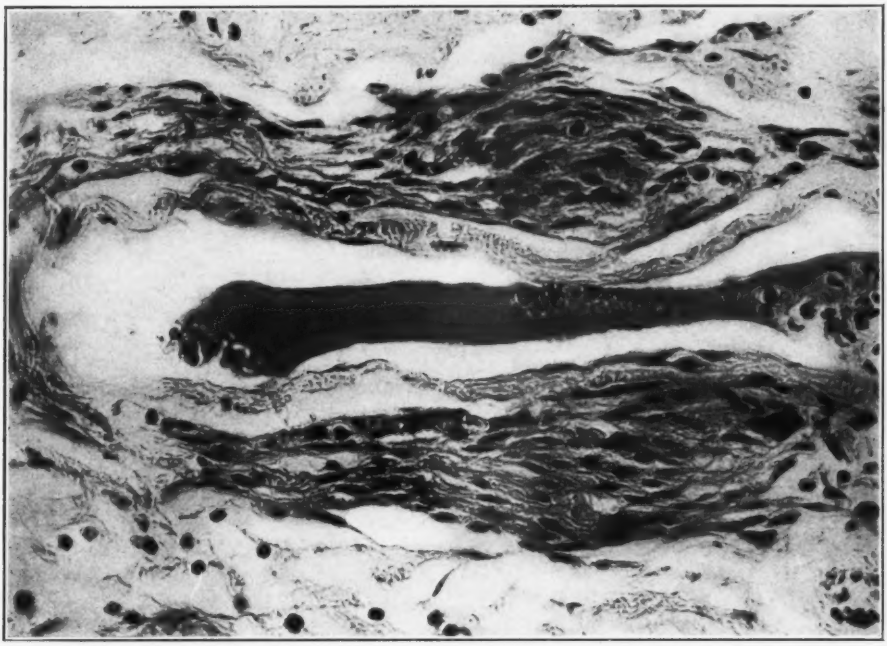
3

Hosoi Meningiomas

PLATE 60

FIG. 4. Photomicrograph of one of the cellular clusters found in the chorioid plexus of the right lateral ventricle. It forms a sort of a sheath around the vessel. It is histologically indistinguishable from the cellular areas of Fig. 3. ×430.

FIG. 5. Photomicrograph, Foot and Mènard method for reticulum. Note the abundance of fine reticular fibrils in intimate association with the tumor cells. ×625.



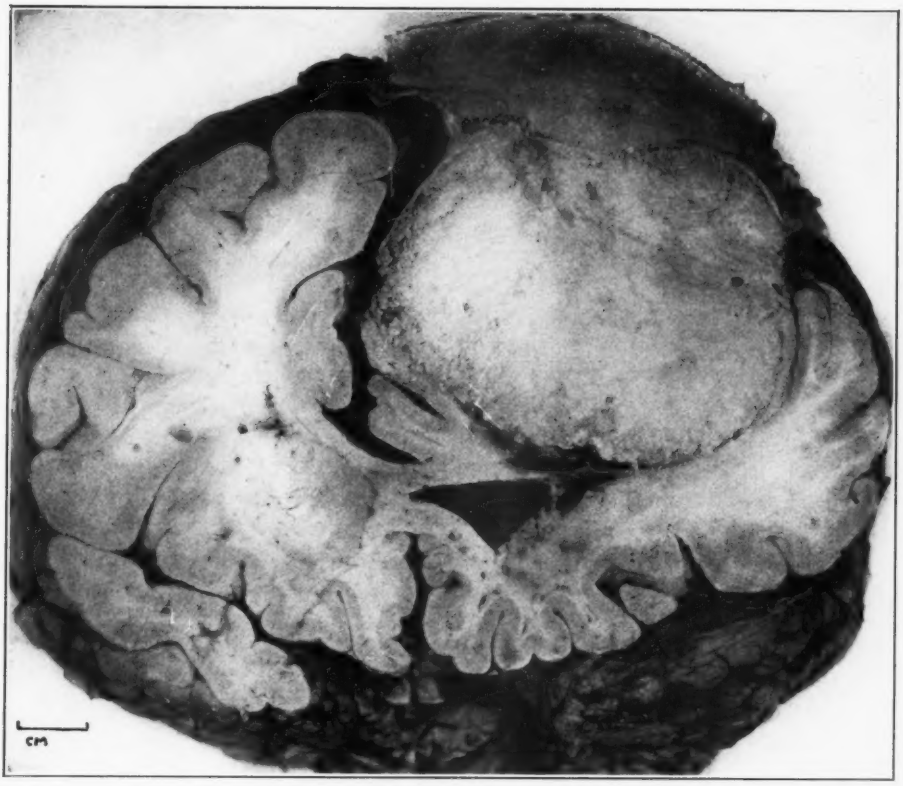
4

5

PLATE 61

FIG. 6. Frontal section of the left frontal lobe showing the marked destruction by pressure atrophy of this portion of the cortex and the production of hyperostosis cranei.

FIG. 7. Photomicrograph of a section through the hyperostosis cranei. Note the invasion of the diploic spaces by the tumor cells. × 100.



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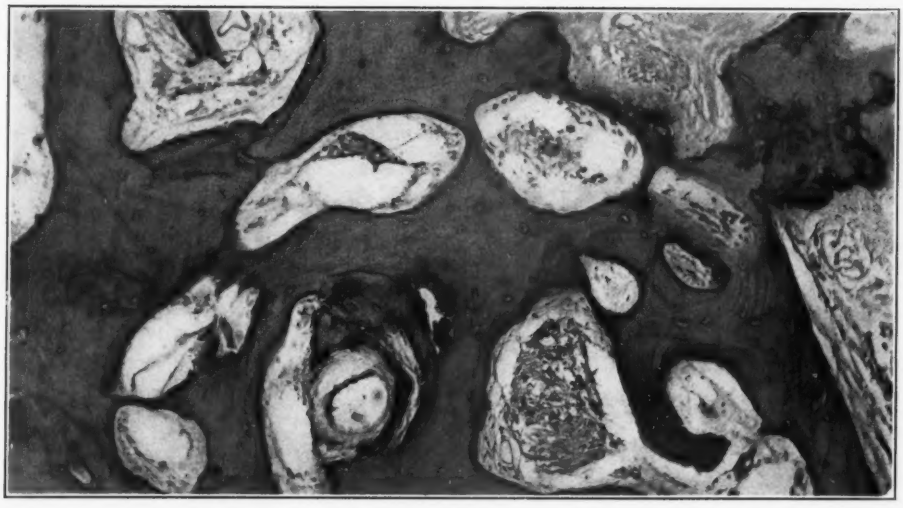

7

CYTOPLASMIC INCLUSIONS PRODUCED BY THE SUBMAXILLARY VIRUS *

E. F. PEARSON

(From the Anatomical Laboratory, Washington University, St. Louis, Mo.)

It has been shown by Cole and Kuttner [1] and by Kuttner [2] that the cellular changes discovered by Jackson [3] in the submaxillary glands of a large proportion of apparently normal guinea pigs are not protozoan parasites but rather alterations caused by a filterable virus. The changes are characterized by marked cytoplasmic and nuclear hypertrophy and by the appearance in the nuclei of acidophilic inclusions which have a distinct resemblance to the intranuclear bodies described by Tyzzer [4] in the cutaneous lesions of varicella — a similarity which was first noted by Goodpasture and Talbot.[5] These intranuclear inclusions in the submaxillary glands of guinea pigs have attracted much attention because it has further been found that they look like inclusions caused by other well recognized viruses such as herpes and virus III, as well as still other nuclear inclusions which occur occasionally in human tissues in the absence of recognizable clinical symptoms (Goodpasture and Talbot, and VonGlahn and Pappenheimer [6]).

In this way attention has been focused on the nucleus to the almost complete neglect of the cytoplasm. This is illogical if we are to gain a true appreciation of the nature of the cellular response to the virus. A reaction is setting in and many cytological observations of fundamental interest have recently been made by Scott [7] and by Scott and Pruett.[8] There remain, however, certain conspicuous cytoplasmic inclusions which thus far have been largely ignored. They were first observed and clearly figured by Jackson who thought that they were "merozoits." Goodpasture and Talbot simply confirmed Jackson's discovery of their occurrence in guinea pigs' submaxillary glands. In the more recent studies of Cole and Kuttner, and of Kuttner, no reference is made to them. The purpose of this paper is to record detailed observations concerning them.

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Morphology

The shape and relative size of the cytoplasmic inclusions in guinea pigs are well illustrated in the photomicrographs (Figs. 10 and 11) which were taken at a magnification of 2000 diameters. The inclusions are clearly visible in the distal parts of the cytoplasm between the nuclei and the lumina of the ducts. They are masses of variable size which in section tend to take a roughly oval shape with their long axes parallel to the cell membrane. This oval shape is represented also in Fig. 4 after the application of the Feulgen reaction.

Many attempts were made to dissect out inclusion-laden cells in order to study the inclusions in the fresh state without the aid of supravital stains, but none of them was successful. In permanent preparations the internal structure of the inclusions depends to some extent upon the technique used.

After fixation in Zenker's fluid and coloration by Giemsa's method the inclusions seem to be made up of clusters of tightly packed and very minute, strongly basophilic particles. That each inclusion mass, or clump of particles, is resilient and fairly dense is shown by the fact that when applied to the nuclear membrane they often indent it because the membrane appears to be more yielding than the inclusion. A good example of such nuclear indentation is shown in Fig. 11.

A wide variety of other fixatives reveals the same particulate appearance irrespective of the stain employed, because morphological characteristics are merely accentuated or suppressed but seldom modified by tinctorial procedures. With some, such as Giemsa's sublimate, the inclusions appear to be more homogeneous in structure. Frequently, and irrespective of the fixation, the centers of the inclusions are less dense than their peripheral parts; indeed the central areas may look like clear vacuoles being devoid of any detectable formed material. This is the appearance represented in Fig. 4. The inclusions are usually limited by a more or less distinct halo.

Microchemistry

These cytoplasmic inclusions are characterized by their great resistance to solvents. No ordinary fixative destroys them. They withstand 80 per cent alcohol, Carnoy's fluid which contains 30 per

cent of acetic acid, and formalin in various concentrations. But it does not follow that they would be equally resistant to solvents applied to them in the fresh state, because Cowdry and Kitchen [9] found that the intranuclear inclusions characteristic of experimental yellow fever in monkeys, though equally resistant to fixatives containing acetic acid were quickly dissolved by the application of 0.05 per cent of acetic acid to the fresh cells.

Viewed in the fixed but unstained state the inclusions are not pigmented, neither are they doubly refractile when examined with crossed nicols. They are strongly basophilic and are thus easily distinguished tinctorially from the acidophilic intranuclear inclusions.

When frozen sections are made after formalin fixation the cytoplasmic inclusions can be tinged only very slightly with Sudan III, whereas neutral fat is strongly colored. Treatment with 2 per cent osmic acid for twenty-four hours results in a slight browning of the inclusions. When osmication is continued for several days a few small black granules make their appearance within the brown-colored inclusions.

Specific tests for mucin yielded rather inconclusive results. It was difficult to color the inclusions in the usual way with mucicarmine but by using a very concentrated sample of the stain they were induced to take a rather dense color which corresponded closely to "Nopal red" in Ridgway's standard color scale,[10] while all the other elements in the tissue were either unstained or but lightly tinged with the dye. This reaction appeared to be specific but should nevertheless be interpreted with caution.

In the first place, Dr. R. R. Bensley has kindly informed me, in a personal communication, that parts of dead cells can often be stained with mucicarmine irrespective of whether they do or do not contain mucus. There are two lines of evidence which indicate that the greatly enlarged duct cells with fully developed cytoplasmic and nuclear inclusions are dead. The first results from the use of methods designed to reveal mitochondria. Fig. 2 represents a cell after preservation in Regaud's fluid and coloration with anilin fuchsin and methyl green. In the original the mitochondria were colored crimson against a light green background. In the figure they are represented in shades of gray and may be recognized by their rod-like shape. It will be seen that, though mitochondria are present in abundance in the uninjured duct cells, they are conspicuous by their absence

in the adjacent greatly hypertrophied cell containing a large intranuclear inclusion and many smaller, spherical, cytoplasmic ones. The second kind of evidence was secured by making intraperitoneal transplantations of parts of submaxillary glands containing inclusions. This was done with three guinea pigs. The transplanted tissues were removed after forty-eight hours and prepared for study. The large cells containing inclusions were found to be unaltered whereas the other cells were in advanced stages of autolysis, which is consistent with the hypothesis that the former were dead to start with. This goes to show that the tinging with mucicarmine may not indicate the presence of mucus.

In the second place, if the inclusions do consist of mucus one would expect them to react in the same way to fixatives and stains as known mucus and granules of mucigen in other parts of the same sections of the salivary glands; but they do not. They are both more resistant to solvents in fixatives and more basophilic than mucus in neighboring cells.

Millon's reagent was then applied but no coloration of the cytoplasmic inclusions could be obtained which was sufficiently intense to justify any conclusion one way or the other.

The Feulgen reaction for thymonucleic acid was tried in accordance with the detailed instructions given by Cowdry [11] and the results are given in black and white in Figs. 3 and 4. The black parts represent the distribution of the deep purple color which is formed in substances said to contain thymonucleic acid. In the cell shown in Fig. 3 this purple color (now black) was limited to the nuclear membrane and to certain masses within the nucleus in close association with the large nuclear inclusion, as well as to the nucleus of the unaltered cell slightly above and to the right. Immediately above the hypertrophied nucleus a single oval cytoplasmic inclusion can be made out. It is in touch with the cell membrane and consequently very near the lumen of the duct. The original faint lilac color which it possessed is here indicated as a light gray. In Fig. 4 also essentially the same very light coloration of the inclusions (below the nucleus) is represented. Evidently thymonucleic acid is either absent in the inclusions or present in very small amounts.

Lastly, the Macallum test for potassium was employed with the modifications advised by Rohdenburg and Geiger.[12] All that can be said is that the black granular deposit which was obtained was

limited to the cytoplasm of both the normal and injured cells. In the latter, however, as illustrated in Fig. 1, it was particularly abundant, especially in the distal region of the cytoplasm between the nucleus and the lumen of the duct, which area is known to contain the largest number of cytoplasmic inclusions.

Incidence

The examination of many guinea pigs of uncertain age was supplemented by the study of three guinea pigs of each of the following ages — 3, 5, 8, and 12 weeks. In this latter series the submaxillary glands were all fixed in Zenker's fluid and colored by Giemsa's stain.

No nuclear or cytoplasmic inclusions were found in the 3 weeks-old guinea pigs. Inclusions were observed only in one of the three guinea pigs killed at the age of 5 weeks, and all of them were nuclear. But all of the 8 and 12 weeks-old animals contained both nuclear and cytoplasmic inclusions. Approximately 10 per cent of the cells possessing intranuclear inclusions in the three guinea pigs of 8 weeks contained cytoplasmic ones, whereas about 50 per cent of them exhibited cytoplasmic inclusions in the three animals of 12 weeks. In support of these findings limited to so few animals it was observed in many instances that old-looking guinea pigs often contained both cytoplasmic and nuclear inclusions, whereas animals weighing less and presumably younger showed only nuclear inclusions.

It is evident that the cytoplasmic inclusions are of definitely restricted incidence in comparison with the nuclear ones. They appear only after the intranuclear inclusions are well formed and after the injured cells have undergone other profound changes, of which may be mentioned great hypertrophy and disappearance of mitochondria. In other words, it is likely that the cytoplasmic inclusions make their appearance at the time or after the death of the affected cells, whereas the intranuclear inclusions are first formed perhaps while the cells are still alive but at any rate before marked enlargement has set in. Figs. 6 and 7, for instance, illustrate intranuclear inclusions in relatively small cells which do not contain typical cytoplasmic inclusions. Even in old guinea pigs where the cellular hypertrophy is extreme, cytoplasmic inclusions are usually, but not

invariably, seen. Sometimes and for no apparent reason they are more abundant than at other times. Cells fully charged with both nuclear and cytoplasmic inclusions may presumably persist for months, even years, without noticeable change. Though apparently dead for the reasons stated, they contain either in their interior or on their surfaces, active virus. In a few, however, the degeneration proceeds further as represented in the photomicrographs, Figs. 12, 13 and 14, and at the same time the cytoplasmic inclusions become less noticeable. Compare these figures with Figs. 10 and 11 which illustrate the height of the reaction in which both types of inclusion are very conspicuous.

This further degeneration of the injured cells is paralleled by non-specific changes in the neighboring duct cells, as seen in Fig. 12. By non-specific I mean that, by contrast, these other cells do not hypertrophy and do not develop inclusions of either kind. Their nuclei are lost by lysis and their cytoplasm fails to stain in the usual way and is replaced by chromophobic watery material. Examination of Fig. 12 shows that the lumen of the original duct is occupied by a very hypertrophied cell with a conspicuous intranuclear inclusion and that the adjacent cells to the left are further degenerated, in this way, than are those to the right. Accompanying such superposed non-specific lesions it is common to find a marked local infiltration consisting principally of lymphocytes and macrophages.

In Fig. 13 the degeneration is not quite so far advanced. The chief points of interest are absence of cytoplasmic inclusions, the extension of the surface of the cell and the failure of the cell to bulge into the lumen. In Fig. 14 the degeneration is so marked that the nuclear inclusion is hardly recognizable, the nuclear membrane itself is partly destroyed and no cytoplasmic inclusions can be made out.

While the vast majority of the injured cells remain in the condition illustrated in Figs. 10 and 11, some proceed further to the state represented in Fig. 14, and a few are definitely removed by desquamation into the lumina of the ducts. Such a cell is shown in Fig. 15. It contains only one cytoplasmic inclusion which is visible in the concavity of the nucleus.

The incidence of the two kinds of inclusions was also investigated in respect to the number of cell types in which they are produced. This was accomplished in three ways. First by the method of in-

tracerebral inoculation introduced for this virus by Cole and Kuttner. They say that "the most striking feature is the presence in the meningeal exudate of large numbers of cells, each of which contains an acidophilic mass within the nucleus. These cells resemble in all particulars the cells containing inclusion bodies which occur in herpes simplex and related conditions . . ."

Following the instructions given by these authors, I injected three young guinea pigs intracerebrally, and under ether anesthesia, with a 10 per cent emulsion in physiological salt solution of the submaxillary glands of several old guinea pigs. The animals were sacrificed seven days later and the intranuclear inclusions mentioned were found in the large mononuclear cells of the exudate, which however contained no trace of cytoplasmic inclusions.

The second method, likewise devised by Cole and Kuttner, was tried without success. It involved the removal, under ether anesthesia, of the submaxillary glands of three young guinea pigs. The wounds healed uneventfully and virus emulsion was injected subcutaneously at frequent intervals over a period of thirty days when the animals were sacrificed and the parotid glands prepared for study. The object was to induce the virus to act upon the parotids in the complete absence of the submaxillary glands, but no inclusions could be found in the parotids. Fortunately, however, Dr. Kuttner very kindly sent me a preparation of the parotid from such an experiment which showed beyond question both cytoplasmic and nuclear inclusions in the duct cells.

The third method of spreading virus action was that of Scott [7] and consisted of the ligation, under ether anesthesia, of the ducts of the submaxillary glands in a series of three young guinea pigs and immediate injection directly into each gland of 0.5 cc. of similar virus emulsion. After sixteen days the glands were removed and prepared for study. Typical cytoplasmic and nuclear inclusions were found in many duct cells as well as in a few of the cells of the serous acini, but nuclear inclusions unaccompanied by cytoplasmic ones were seen in addition in smooth muscle cells, fibroblasts, endothelial cells and large mononuclear cells.

Clearly, therefore, the formation of cytoplasmic inclusions is a much more restricted mode of response to the virus than that of the development of intranuclear inclusions when a variety of cell types is considered. In guinea pigs the cytoplasmic inclusions are de-

invariably, seen. Sometimes and for no apparent reason they are more abundant than at other times. Cells fully charged with both nuclear and cytoplasmic inclusions may presumably persist for months, even years, without noticeable change. Though apparently dead for the reasons stated, they contain either in their interior or on their surfaces, active virus. In a few, however, the degeneration proceeds further as represented in the photomicrographs, Figs. 12, 13 and 14, and at the same time the cytoplasmic inclusions become less noticeable. Compare these figures with Figs. 10 and 11 which illustrate the height of the reaction in which both types of inclusion are very conspicuous.

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Clearly, therefore, the formation of cytoplasmic inclusions is a much more restricted mode of response to the virus than that of the development of intranuclear inclusions when a variety of cell types is considered. In guinea pigs the cytoplasmic inclusions are de-

veloped in the duct cells of the parotid and of the mucous and serous portions of the submaxillary gland as well as in the serous acinous cells of the latter. They are never seen in the absence of intranuclear inclusions.

Discussion

What then is the status of these cytoplasmic inclusions? Until they have been seen in guinea pigs in injuries other than those caused by the submaxillary virus we may logically regard them in a provisional way as specific of its action. This specificity is however one-sided, for though the presence of cytoplasmic inclusions points to the presence of the virus, their absence does not mean that the virus is likewise absent; it indicates merely that the virus is weak. This statement is justified in view of Cole and Kuttner's experiments. Beginning with a saline emulsion of submaxillary glands containing many cytoplasmic and nuclear inclusions, it was a simple matter for them and for Scott and for me to create by intracerebral injection in guinea pigs a fatal meningitis characterized by an abundance of intranuclear inclusions without any cytoplasmic inclusions. But the second intracerebral passage very seldom if ever results in a distinct infection in spite of the large number of intranuclear inclusions in the material passed. Indeed Cole and Kuttner were only able to maintain the virus in a few serial transfers by alternating their sites of inoculation between testicle and brain and skin and brain. They do not state whether cytoplasmic inclusions occur in the testicle and skin. If they had been conspicuously present, reference would probably have been made to them. Summarizing the situation, it is safe to say that the virus has not yet been maintained by direct passage in unlimited series in any tissue except in the salivary glands in which the formation of the cytoplasmic inclusions is such a very conspicuous and apparently unavoidable feature of the cellular response.

It is possible therefore that the development of cytoplasmic inclusions is in some way concerned with the continuation of the virus in nature, or it may be that the cytoplasmic inclusions are merely incidental by-products of its action. Both hypotheses are rational in the light of our present scanty information. In terms of the latter hypothesis the conditioning factors in the formation of the cytoplasmic inclusions cannot as yet be given in detail. It may be a

question of the relative availability of material for the building up of the inclusions. Such material may not be present in sufficient amounts to form cytoplasmic inclusions in the large mononuclear, endothelial and other cells which habitually develop only intranuclear inclusions. Or again, it may be a case of the greater retention in the duct cells of material more rapidly removed from the other cells. Certain it is that the development of cytoplasmic inclusions in the duct cells of the submaxillary glands and their absence in other kinds of cells affected by the virus is but one of many fundamental differences in response. A second is the great hypertrophy of the duct cells and a third is their death and retention in the tissues without essential modification for months, perhaps for years, whereas the other kinds of cells are enlarged but little and are soon removed by phagocytic action. Persistence of the virus is provided for by cells which carry cytoplasmic inclusions in addition to nuclear ones.

Comparing now these cytoplasmic inclusions with other cytoplasmic inclusions described in the literature as caused by other kinds of viruses, we find no possibility of confusion. Like cytoplasmic inclusions in general as discussed by Cowdry [13] they are rather resistant to solvents contained in fixatives so that no special technique is required for their demonstration. They are basophilic like some of the inclusions in infectious myxomatosis of rabbits and trachoma bodies, but here the similarity ends owing to their distinctive morphology. Each inclusion is made up of many fine particles, as is the case in birdpox; but in the submaxillary disease the lipoidal component is wanting. From typical large Negri bodies they are easily distinguished by the absence of any acidophilic material. Finally it may be said that the submaxillary cytoplasmic inclusions are not made up of the heterogeneous material which is typical of Guarnieri bodies; but like the Guarnieri bodies (Cowdry,[14] Fig. 37) they are of such firm consistency that they indent the nuclei when in contact with them.

The submaxillary virus is rightly grouped with viruses like those of herpes, chickenpox, Borna disease and other conditions which are characterized only by the formation of intranuclear inclusions. The cytoplasmic inclusions described in this paper are not so inseparable from the action of the virus as to justify the reclassification of the virus with those of variola and paravaccinia which con-

stantly produce both cytoplasmic and nuclear inclusions in all susceptible cells.

Whatever the significance of these cytoplasmic inclusions may be in the guinea pig, the fact that other similar cytoplasmic inclusions have been clearly described and illustrated by Wilson and Du Bois[15] in greatly enlarged duct cells of the submaxillary and parotid glands in a case of keratomalacia is of considerable interest because the inclusions afford another kind of cellular response which is common to guinea pigs and humans. A comparison of two photomicrographs by Wilson and Du Bois (Figs. 2 and 3[15]) with my photomicrographs (Figs. 10 and 11) shows that the similarity, not only in the cytoplasmic inclusions, but also in the nuclear ones and indeed in all other visible cellular attributes, amounts almost to identity. Study of the actual preparations side by side was made possible by the kindness of Dr. S. B. Wolbach in sending three specimens which form part of the material which will constitute the basis of a report from the department of pathology of the Harvard Medical School. The first specimen is of the submaxillary gland from the case described by Wilson and Du Bois (A-1009); the second of a parotid gland from a Children's Hospital autopsy (A-24-28) and the third of a lung from the case described by Goodpasture and Talbot.[5] In the first two specimens I found cytoplasmic inclusions indistinguishable from those in guinea pigs. Rather less distinct cytoplasmic structures were observed in the third preparation of the lungs. But it is probable that identical cytoplasmic inclusions occurred in the lungs also, because Goodpasture and Talbot refer to the existence in them of cytoplasmic bodies similar to those reported in the guinea pig's submaxillary gland.

It is probable that others before Goodpasture and Talbot, notably Jesionek and Kiolemenoglou[16] have observed the coexistence of nuclear and cytoplasmic inclusions in human salivary glands. The available evidence is, however, against the possibility that vitamine A deficiency is the causative factor in their production, which is suggested by their abundance in the case of keratomalacia, for the changes which result from experimental vitamine A deficiency have been carefully investigated by Wolbach and Howe,[17] and others, without bringing to light any inclusions, either nuclear or cytoplasmic. Far more likely is it that the inclusions in humans, as in guinea pigs, are caused by the action of a virus. The fact that the

same duct cells of the same glands are affected, and, further that they are altered, as far as we can tell in precisely the same way, indicates that the guinea pig and human viruses are very similar, if they are not one and the same. We have other instances of individual viruses which can be induced to bring about similar cellular modifications in the cells of humans and guinea pigs (herpes, vaccinia, rabies, etc.,) but none are recognized which do so naturally in a spontaneous way.

Results

The cytoplasmic inclusions which are developed in the duct cells of the submaxillary glands of guinea pigs as a result of the action of the submaxillary virus are formed later than are the nuclear inclusions. They are also more restricted in distribution, having been found only in the ducts of the mucous and serous portions of the submaxillary, occasionally in the acini and in the ducts of the parotid; whereas the intranuclear inclusions may in addition be produced in endothelial cells, fibroblasts, smooth muscle cells and mononuclear leucocytes. The cytoplasmic inclusions are spherical or oval structures which vary in size from a fraction of a micron up to 6 to 8 microns in diameter. In the fully developed state the average inclusion is about 3 microns in its long axis. The inclusions are made up of many much smaller individual particles which are densely packed together. Like the cytoplasmic inclusions in other virus diseases, these inclusions are characterized by their relative insolubility in ordinary fixatives. They are basophilic in reaction and do not contain fat or lipoid in detectable amounts. They are, moreover, indistinguishable from certain cytoplasmic inclusions of rare occurrence in human submaxillary glands.

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DESCRIPTION OF PLATES

PLATE 62

All of these figures were originally drawn in colors with the aid of a camera lucida. They have been reduced to black and white by photography.

FIG. 1. An inclusion-laden cell from the secretory duct of the submaxillary gland of an adult guinea pig. The Macallum test for potassium revealed deposits localized in areas which correspond topographically to those occupied by the cytoplasmic inclusions (compare with Fig. 8). Potassium deposits are black in the figure. Two adjacent normal cells are represented above the cell containing the nuclear inclusion. × 2000.

FIG. 2. An affected cell from the submaxillary gland of an adult guinea pig. The gland was fixed in Regaud's fluid and stained with anilin acid fuchsin and methyl green to reveal mitochondria, which appear as black, straight and slightly curved rods. The normal secretory duct cells have abundant mitochondria, whereas the inclusion-laden cell shows a complete absence of these cytoplasmic bodies. × 2000.

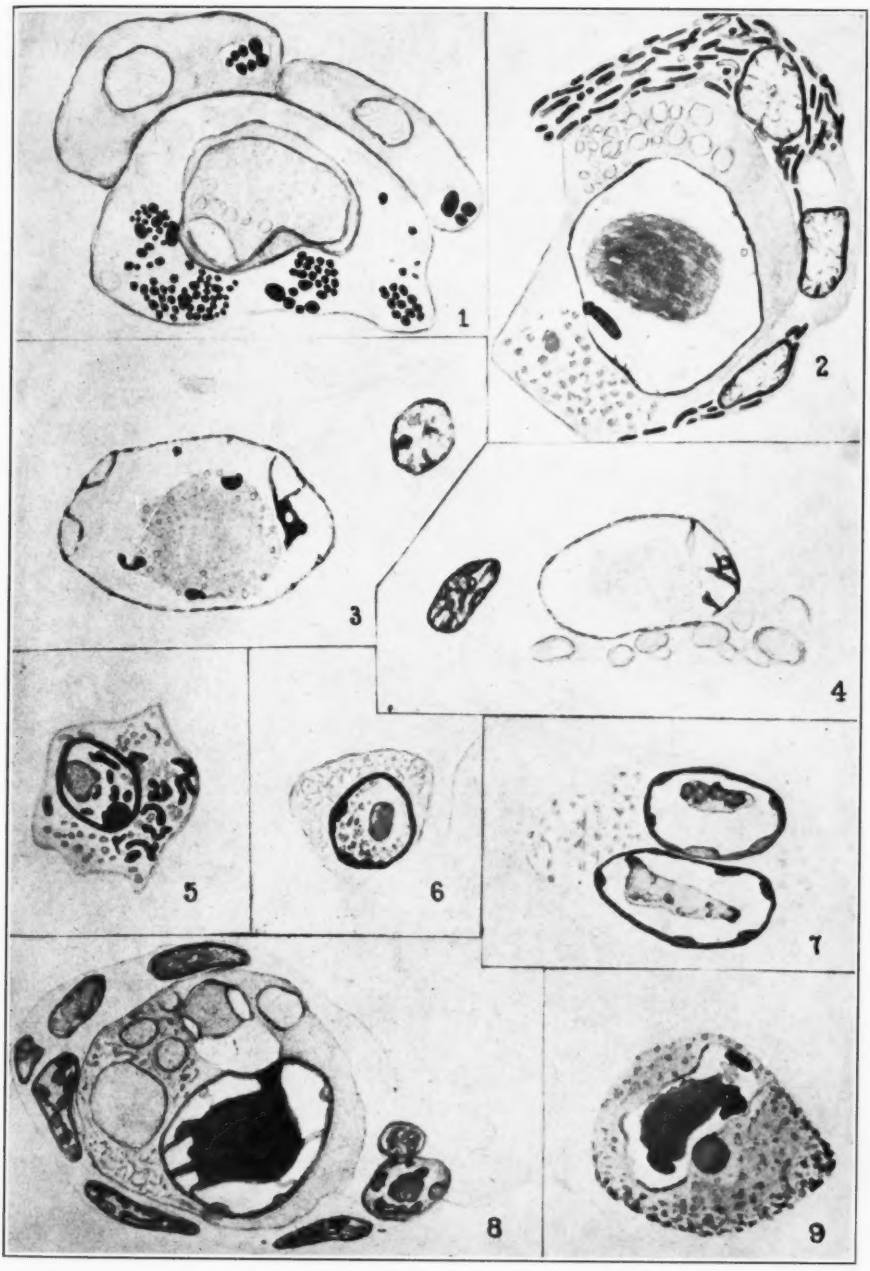
FIGS. 3 and 4. Affected cells from the submaxillary gland of an adult guinea pig. The Feulgen reaction for thymonucleic acid has been applied to these cells. In Fig. 3 the intranuclear inclusion stains but faintly, which is in contrast to the strongly positive particles of chromatin adhering to it. A cytoplasmic inclusion is shown slightly tinged in the upper portion of the cell. In Fig. 4 the nuclear inclusion is but faintly tinged with the dye as is the group of cytoplasmic inclusions. The nuclei of normal adjacent secretory duct cells give a strongly positive reaction as can be seen in the figures. × 2000.

FIGS. 5 and 6. Inclusion-bearing acinar cells of the submaxillary gland of an adult guinea pig. The degree of nuclear hypertrophy is not so marked as is that of the secretory duct cells. In Fig. 5 the cell shows a strongly basophilic reaction of the cytoplasm but no visible cytoplasmic inclusions. Giemsa's stain. × 1500.

FIG. 7. A binucleate fibroblast, each nucleus of which contains an inclusion body. There are no cytoplasmic inclusions present. Taken from a section of the submaxillary gland of an adult guinea pig. Giemsa's stain. × 2000.

FIG. 8. An inclusion-laden cell of an intercalated duct from the submaxillary gland of an adult guinea pig. Note the particularly large and well developed cytoplasmic inclusions. The affected cell has completely plugged the intercalated duct. Giemsa's stain. × 2000.

FIG. 9. An affected cell found in the duct of the minor sublingual gland of an adult guinea pig. A cytoplasmic inclusion may be seen adjacent to the nucleus. Hematoxylin and eosin. × 1500.



Pearson

Inclusions Produced by Submaxillary Virus

PLATE 63

All of these figures are photomicrographs taken by Mr. Louis Schmidt of the Rockefeller Institute at a magnification of 2000 diameters from preparations fixed in Zenker's fluid and colored by Giemsa's stain.

FIG. 10. Shows two cells containing both cytoplasmic and nuclear inclusions on opposite sides of a secretory duct.

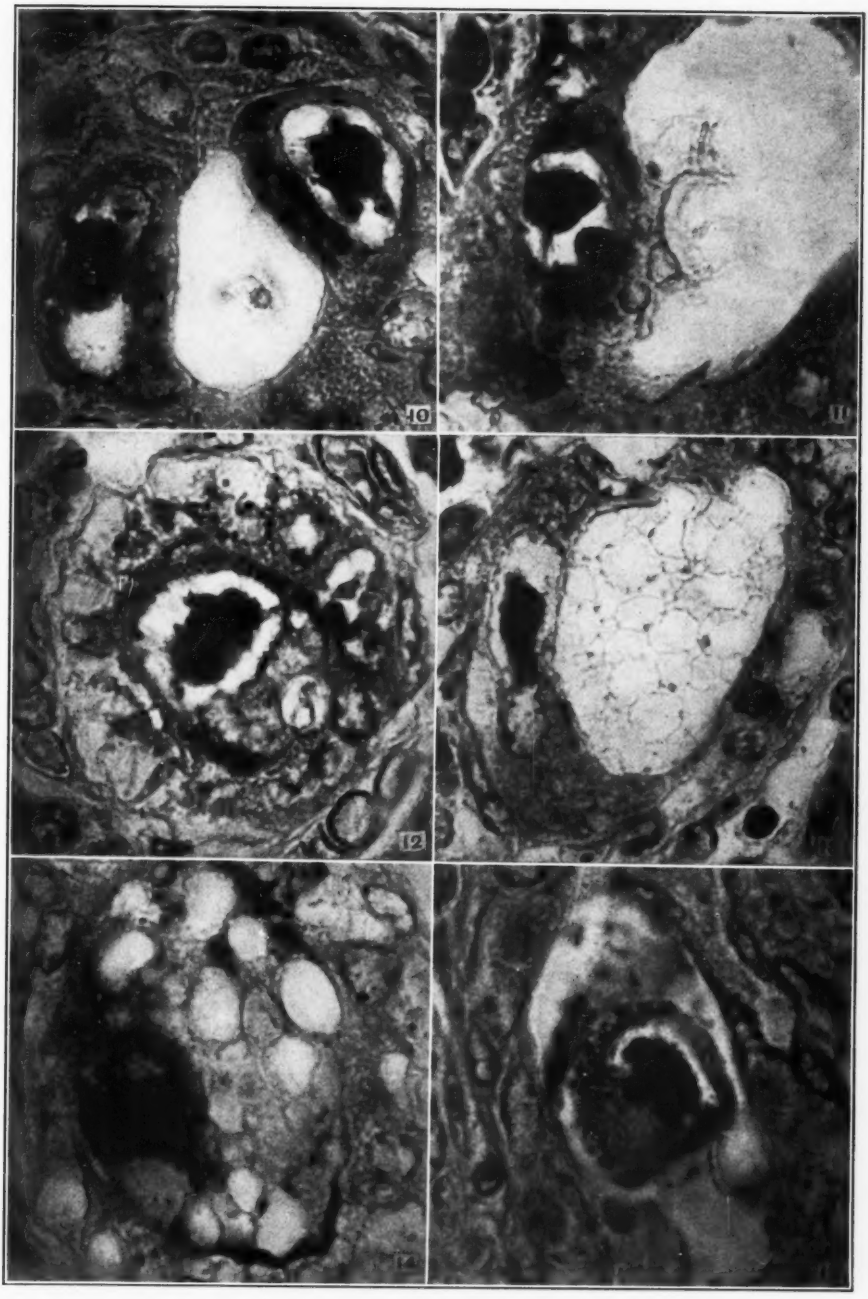
FIG. 11. Represents a single cell laden with both types of inclusions. The cytoplasmic inclusions exercise pressure on the nuclear membrane and indent it.

FIG. 12. Shows a duct almost completely blocked with a greatly hypertrophied cell containing a large intranuclear inclusion. Cytoplasmic inclusions are not visible. The unenlarged duct cells are severely injured, particularly to the left.

FIG. 13. Represents likewise an enlarged cell possessed of a distinct nuclear inclusion but no cytoplasmic ones. The condition is unusual because the cell does not bulge into the lumen.

FIG. 14. Illustrates a very degenerated cell bordering the lumen in which neither nuclear nor cytoplasmic inclusions can be clearly distinguished.

FIG. 15. Shows an inclusion-bearing cell which has been cast off into the lumen. A single spherical cytoplasmic inclusion can be seen in the concavity of the nucleus.



Pearson

Inclusions Produced by Submaxillary Virus

STUDIES IN THE ETIOLOGY OF SIMPLE GOITER *

BRUCE WEBSTER, M.D., AND ALAN M. CHESNEY, M.D.

(From the Department of Medicine of the Johns Hopkins University School of Medicine, Baltimore, Md.)

INTRODUCTION

In a previous communication [1] we have reported the occurrence of goiter in a colony of rabbits maintained upon a diet consisting almost exclusively of cabbage. The condition was identified as simple or endemic goiter. The microscopic picture usually presented was that of the typical *struma diffusa parenchymatosa*. In view of the multiplicity of etiological factors with which simple goiter is commonly accredited, it was considered advisable to attempt to rule out some of these as contributory factors in the present epidemic. This communication deals with a series of experiments which were carried out in an effort to determine whether or not the cabbage diet was the sole etiological factor in this instance and, if not, what rôle certain other factors played in the production of goiter. Since goiter occurred with great regularity in all stock rabbits kept under standard conditions in our laboratory, it is considered advisable to describe these standard conditions briefly.

The rabbits were housed in quarters on the eighth floor of the dispensary building of the Johns Hopkins Hospital. The room is well ventilated and well lighted, having a southern and eastern exposure. The cages are supported on metal racks, three tiers high with ample ventilation space between individual cages. The standard cage is of metal and measures 45 by 30 by 30 cm. The front and top are made of wire mesh. The bottom of the cage is covered with shavings which are changed once or twice weekly. The standard diet consists of a daily ration of approximately 250 gm. of cabbage and a weekly ration of approximately 20 gm. of hay and 50 gm. of oats. The cabbage was procured from various regions in the Eastern United States, ranging between Florida and New York state with the season. Water was not given on the standard diet. No special breed of rabbits was used, the stock being procured

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largely from dealers in Maryland and Pennsylvania. All animals were examined on admission and were found to be clinically negative as regards thyroid enlargement.

All of the animals used in the experiments described below were of known stock and age. The animals in each experimental and control group were of the same age and the groups were so arranged that the number of males and females was the same in each group. Because of this uniformity of experimental material, absolute thyroid gland weights are given throughout, instead of thyroid gland, body weight ratios.

Experimental

Experiment No. 1: In view of the extensive work of McCarrison [2] and others on the relationship of food contamination to the etiology of goiter, an attempt was made to determine whether or not this factor played any part in the present epidemic. Accordingly, a special system of caging was instituted with the idea of removing, as far as possible, the factor of fecal contamination of the food. These cages were of metal and measured 61 by 46 by 31 cm. The top and front were of wire mesh. The bottom consisted of a removable metal pan over which was placed a grid of coarse wire mesh. Through this grid the urine and feces dropped to the pan below. The pans were so arranged that they drained into a central drainage system. In this way, the bottom of the cage, on which the animal rests, was always clean and dry. At frequent intervals the rabbits were removed and the interior of the cages was washed by means of a hose. Food was placed in glazed earthenware cups, 3 inches high. These cages were placed in a well ventilated, well lighted part of the animal room. By this manner of caging, fecal and urinary contamination of the food was almost entirely eliminated.

Five litters, consisting of thirty-two rabbits of approximately the same age, were used for this experiment. Sixteen rabbits were placed in the special cages described above. The remainder were housed in standard cages and were intended to serve as a control series. The litters were divided into approximately equal parts. The diet in both instances was identical, the standard laboratory diet being used. The mortality from intercurrent infections was high during the course of this experiment. At the end of approxi-

TABLE I

Incidence of Goiter in Rabbits Maintained in Two Types of Cages

Group I — Special Cages					Group II — Standard Cages				
Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid	Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid
	gm.					*gm.*			
2111	2.5	345	sacrificed	marked hyperplasia	2107	1.2	345	sacrificed	marked hyperplasia
2112	14.0	345	"	" "	2108	1.3	345	"	" "
2113	2.8	345	"	" "	2109	8.4	345	"	" "
2114	2.8	345	"	" "	2110	3.5	345	"	" "
2136	0.8	330	"	hyperplasia	2140	2.5	345	"	" "
2188	0.5	325	"	"	2190	1.2	345	"	" "
2189	0.9	325	"	"	2191	0.8	345	"	" "
2182	0.4	325	"	"	2185	2.7	345	"	" "
2195	1.8	325	"	"	2139	3.8	276	pneumonia	" "
2196	1.2	270	pneumonia	"	2192	0.65	258	"	hyperplasia
2138	0.3	97	diarrhea	slight hyperplasia	2137	0.6	172	"	"
2135	0.4	87	caseous abscess	" "	2197	0.6	141	"	"
2183	0.3	75	diarrhea	" "	2199	0.4	88	diarrhea	slight hyperplasia
2187	0.3	72	"	" "	2198	0.2	55	"	normal
2184	0.1	60	"	normal	2186	0.7	52	"	hyperplasia
2194	0.2	50	pneumonia	"					

mately three hundred and forty days, the animals still living were sacrificed and autopsied. Table I shows the results of the above experiment.

It will be observed from an inspection of Table I, that goiter developed in the animals kept in the special cages where fecal and urinary contamination was reduced to a minimum (Group 1), as readily as in the animals kept in cages where there was abundant opportunity for fecal and urinary contamination. The average weight of the thyroid glands at the termination of the experiment was 2.83 gm. for the group housed in the special cages, and 2.70 gm. for those housed under standard laboratory conditions.

Experiment No. 2: Since water has been associated with the etiology of simple goiter by all peoples from the remotest times [3] it was considered advisable to determine whether or not the absence of water was a factor in the present epidemic, and at the same time to find out if the traces of iodine contained in Baltimore city tap water * were sufficient to protect the animals against a powerful goitrogenic influence such as we were dealing with in this instance. Thirty rabbits of approximately the same age and from the same source were divided into three equal groups. All were placed on the standard cabbage diet and were housed under the standard laboratory conditions. Group 1 was constantly supplied with freshly distilled water in glazed earthenware containers. Group 2 was similarly supplied with Baltimore city tap water. Group 3 served as a control series and was given no water to drink. At the end of one hundred and twenty-five days all the animals were sacrificed and autopsied. Table II shows the results of this experiment.

This experiment was terminated at an earlier date than in the case of the preceding one, hence the thyroid weights were smaller. Previous experience had shown that time is an important factor in the development of the larger goiters in rabbits maintained on the goiter-producing diet. The table shows that the average weight of the thyroid gland in Group 1 (which received distilled water) was 0.57 gm., while the average weight in Group 2 (which received tap water) was 0.53 gm. In the control series the average weight of the thyroid gland was 0.67 gm. Microscopic sections of the thyroid glands of all animals sacrificed at the termination of the experiment showed varying degrees of hyperplasia.

* Two parts per billion, as estimated in laboratories of City Water Department.

TABLE II

Effect of Adding Water to the Diet on the Incidence of Goiter in Rabbits

Group 1 — Distilled Water Series					Group 3 — Control Series					Group 2 — Tap Water Series				
Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid	Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thryoid	Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid
	gm.					*gm.*					*gm.*			
2397	0.80	125	sacrificed	hyperplasia	2400	0.70	125	sacrificed	hyperplasia	2390	0.25	125	sacrificed	slight hyperplasia
2380	0.80	125	"	"	2401	0.60	125	"	"	2391	0.30	125	"	"
2382	0.40	125	"	"	2402	0.90	125	"	"	2392	0.55	125	"	hyperplasia
2383	0.30	125	"	slight hyperplasia	2404	0.50	125	"	"	2393	0.55	125	"	"
2384	0.40	125	"	hyperplasia	2405	0.50	125	"	"	2394	0.65	125	"	"
2385	1.40	125	"	"	2406	0.65	125	"	"	2395	1.00	125	"	"
2386	0.45	125	"	"	2407	0.60	125	"	"	2396	0.30	125	"	slight hyperplasia
2387	0.55	125	"	"	2408	0.50	125	"	"	2397	0.60	125	"	hyperplasia
2389	0.50	125	"	"	2410	1.40	125	"	"	2398	0.65	125	"	"
2388	0.10	20	pneumonia	normal	2409	0.40	34	pneumonia	slight hyperplasia	2399	0.45	125	"	"

Experiment No. 3: An attempt was made to demonstrate the effect of iodine prophylaxis against an active goitrogenic agent such as the cabbage diet. Four litters consisting of sixteen rabbits, were divided into two equal groups containing representatives of each litter. These animals were all placed in standard cages and maintained on the standard cabbage diet. Group A received 7.5 mg. of iodine per week by mouth. Group B served as a control series and received no iodine. At the end of approximately four hundred days, all of the surviving animals of Group B had visible and readily palpable goiters, while in none of the Group A animals could the thyroid gland be felt at this period. The rabbits were then sacrificed and autopsied. Table III shows the results of this experiment.

Here it can be seen that all of the animals in Group A had thyroid glands which were within the normal weight range (average 0.25 gm.), while all those in Group B had moderate-sized goiters, the average thyroid gland weighing 2.3 gm.

During the course of the above experiments, several striking aspects of the disease manifested themselves. There was considerable individual susceptibility on the part of certain animals toward the goitrogenic agent. Thus, in Table III, Group B, one sees that rabbit No. 2029 had a thyroid gland which weighed 7.3 gm. while numbers 2028, 2030 and 2031, which were from the same litter and were kept under identical conditions, had thyroid glands weighing 1.8, 1.4 and 1.4 gm. respectively. This same variation may be noted in many of the other tables. A marked seasonal variation was also noted. In animals brought into the laboratory in the late autumn or winter, clinically detectable goiters developed much more quickly than in those procured in the spring or summer months. Similarly, some of the large goiters tended to decrease in size slightly during the spring and summer. Throughout the present epidemic no greater incidence in females than in males has been noted. There is suggestive evidence that young rabbits are more susceptible to the goitrogenic influence than adult ones. No variation in the incidence of goiter has been noted among the different breeds of rabbits.

TABLE III

Showing the Effect of the Addition of 7.5 mg. of Iodine Per Week to the Diet on the Incidence of Goiter in Rabbits

Group A — Standard Diet plus 7.5 mg. Iodine per week					Group B — Standard Diet				
Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid	Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid
	gm.					*gm.*			
1994	0.30	420	sacrificed	colloid increased, no hyperplasia	1998	1.75	420	sacrificed	extreme hyperplasia
1996	0.25	420	"	"	2000	2.0	420	"	" "
1997	0.30	420	"	"	2001	1.6	420	"	" "
2033	0.20	400	"	"	2028	1.8	400	"	" "
2035	0.30	400	"	"	2029	7.3	400	"	" "
1995	0.20	200	pneumonia	"	2030	1.4	400	"	" "
2032	0.30	130	"	"	2031	1.4	400	"	" "
2034	0.10	25	none found	"	1999	1.1	225	pneumonia	" "

Discussion

The experiments outlined above appear to indicate that the major etiological factor in the epidemic of simple goiter under investigation, is a nutritional one. The cabbage diet, on which the animals were maintained, apparently exerted a very active goitrogenic influence.

These experiments are not in accord with the extensive investigations of McCarrison,[2] in which he attempted to show that unhygienic surroundings and fecal contamination of food were important causative factors in endemic and experimental goiter. In Experiment No. 1 there was no greater tendency to thyroid hyperplasia when the animals were kept under conditions permitting easy contamination of food than when they were maintained in the special cages under the best possible conditions.

Drinking water has been associated with the etiology of simple goiter by countless writers on the subject.[3] In this instance, since goiter occurred when the animals were given no water to drink, one might conceive of the goitrogenic factor as being due to the absence, rather than the presence of, some water-borne substance. Experiment No. 2, however, shows that the addition of either tap or distilled water to the diet has little or no effect on the goitrogenic factor. The slightly lower level of the average thyroid gland weights of the groups receiving water (0.57 and 0.53), as compared with those of the control group (0.67), is well within the range of accuracy of such a method of observation. The amount of iodine or other inorganic substances in the tap water of Baltimore city apparently is not sufficient to cause any detectable effect different from that given by distilled water.

As Marine has repeatedly shown, iodine in sufficient quantities will protect against all known goitrogenic agents. Experiment No. 3 shows clearly that 7.5 mg. of iodine per week was sufficient to afford the animals complete protection for a period of over one year. It is probable that much smaller amounts would have sufficed. The traces of iodine contained in the drinking water exerted no demonstrable effect. The exact amount necessary to protect lies somewhere between those two extremes.

The experiments outlined above appear to rule out fecal and urinary contamination of food, and deficiency in water-borne sub-

stances as accessory factors in the etiology of the present epidemic of simple goiter. It would appear that the cabbage diet on which the animals were maintained contains some powerful goitrogenic agent. Further, our experience has been that there is considerable seasonal variation in the incidence of goiter in these animals. This could be due to seasonal increase in the goitrogenic factor or to variation in the animals' susceptibility at certain time periods. The extreme variation in susceptibility of individual animals from the same litter is of great interest. One has to presuppose a so-called "constitutional factor" here which may conceivably operate through other endocrine glands and exert a protective influence, in certain instances, against the goitrogenic agent.

Since the above experiments were concluded, Marine, Baumann and Cipra [4] have added considerable light to our knowledge of cabbage as a goitrogenic agent. They have confirmed our observation that a cabbage diet will produce thyroid hyperplasia in rabbits, and have further shown that other members of the Brassica group will also produce goiter. They have suggested that cabbage acts as a goitrogenic agent by depleting the thyroxin store in the thyroid, thus producing a relative iodine insufficiency in the animal, which in turn causes hyperplasia of the thyroid gland. Marine's suggestion that this is brought about by some powerful reducing substance contained in the cabbage seems probable, and offers a possible explanation of many of the hitherto seemingly unrelated etiological factors of simple goiter.

Summary

Further investigations into the etiological factors involved in an epidemic of simple goiter in rabbits are reported. A diet which consists almost exclusively of cabbage appears to be the major etiological factor. Fecal and urinary contamination of food seemingly play no rôle in the present epidemic. The addition of water (either tap or distilled) to the diet exerts no appreciable protective influence against the goitrogenic agent. Iodine, administered orally in quantities of 7.5 mg. per week will completely protect the animal against the goiter-producing factor. There is no evidence that the minute traces of iodine contained in Baltimore city tap water exert any detectable protective influence. The goitrogenic agent is much

more active in winter than in the summer months. This goiter-producing factor appears to be a nutritional one and may act through the oxidation-reduction systems of the body.

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NEPHROSIS IN MULTIPLE MYELOMA *

DAVID PERLA, M.D. AND LAURENCE HUTNER, M.D.
(From the Laboratories of the Montefiore Hospital, New York City)

Although the association of pathological changes in the kidney with multiple myeloma has long been recognized, the exact nature of these changes has not been sufficiently emphasized. In the two instances of multiple myeloma reported in the present communication, a severe nephrosis complicated the disease.

In a careful survey of the literature by Wallgren,[1] and Geschickter and Copeland[2] an attempt was made to study the kidney lesions. Of the vast number of communications on the subject of multiple myeloma, descriptions of the morphology of the kidney were found in less than 20 per cent of the instances. In most of these the descriptions were inadequate. Since the more recent knowledge of the nephroses was entirely unknown to the earlier pathologists, it is reasonable to assume that its appearance was often overlooked or certainly misinterpreted. From the description in the case reports of Scheele and Herxheimer,[3] Austin[4] and Beck and McCleary,[5] a marked destruction of tubules was noted with secondary interstitial changes. Thannhauser and Krauss[6] in 1921 report in considerable detail changes in the kidney indicative of a nephrosis. The kidneys were small and white. Microscopically they showed a diffuse, severe degenerative change of the entire tubular system with very little involvement of the glomeruli. The tubules were replaced by a richly cellular connective tissue. In addition there were small foci of lymphocytes. In some areas tubules were recognizable but showed degenerative changes. Peculiar lamellated casts were seen in the lumina of the intact tubules. On the outer layer were occasional foreign body giant cells. Thannhauser and Krauss believe these structures are concretions of serum protein and Bence-Jones albumose. Clinically, the patient had had evidence of nephrosis. This is the first instance of a pure nephrosis in multiple myeloma noted in the literature.

McConnell[7] in a report of an instance of multiple myeloma describes extensive tubular destruction in the kidneys with hyalinized glomeruli as well as calcification in the tubules. He erroneously

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interpreted this as chronic parenchymatous nephritis. Kleine [8] in a recent article described a large white kidney with narrow obscure cortex in a multiple myeloma. He found a marked nephrosis with lamellated casts in the intact tubules and syncytial giant cells at their periphery. These casts were digested by trypsin, were insoluble in alcohol, water and weak acid, and dissolved with antiformin. He interpreted the lesions as parenchymatous and interstitial nephritis. Bannick and Greene [9] reported in considerable detail the clinical histories of thirteen instances of Bence-Jones albumosuria, associated with renal insufficiency. There was marked secondary anemia, non-protein nitrogen retention, low specific gravity of the urine with no hematuria and usually without hypertension or retinitis. Although they did not report any autopsy findings, they believed the condition was associated with extensive tubular destruction with subsequent fibrosis or pyelonephritis. Arteriosclerosis and hypertension occurred in some instances.

CASE 1.

Clinical History: H. A., age 43 years, was admitted to the medical service of Montefiore Hospital on March 19, 1929 with the complaints of pain in the chest, cough and loss of weight of six months duration. The present illness began six months ago with knife-like pains in the left lower chest radiating to the back and neck. The pain increased on exertion. During the last few weeks he had had weakness, dizziness on exertion, anorexia, constipation and, during the last four days, vomiting. The patient was well built. His skin had a waxy pallor. Tender areas were felt over the sixth and seventh ribs on the anterior chest wall. There was a short systolic apical murmur with no enlargement of the heart. The blood pressure was 130 / 80. Examination of the lungs, abdomen and extremities revealed no abnormalities. Rectal examination showed a small prostate free of nodules.

Laboratory Data: Blood Wassermann was negative. Urea nitrogen 64, creatinin 5.5, calcium 14.6, phosphorus 6.2, basal metabolism rate minus 25 per cent. Examination of blood on March 21st: red blood cells 2,560,000, hemoglobin 48 per cent (Dare), white blood cells 6,400, polymorphonuclears 62 per cent. May 2nd: red blood cells 1,150,000, hemoglobin 15 per cent.

The urine contained large amounts of albumin and of Bence-Jones albumose. The sediment contained granular casts and white blood cells. Concentration (dry) showed a specific gravity of 1011, 1010, 1011. Roentgen-ray examination revealed numerous areas of rarefaction in the skull, ribs, seventh dorsal vertebra and pelvis.

Clinical Diagnosis: Multiple myeloma with Bence-Jones proteinuria and nephrosis. The patient received a series of five X-ray treatments. Two months after admission, hemorrhages from the gums and in the eye-grounds were noted. The patient became progressively weaker, developed twitching movements, uremic manifestations, and died.

Autopsy Report

Anatomical Diagnoses: The anatomical diagnoses were: Multiple myeloma involving ribs, vertebrae, femora, ossa innominata, liver and spleen; chronic nephrosis with contraction of the kidneys; fatty metamorphosis of the heart; parenchymatous degeneration of the viscera; acute splenic tumor; edema of the lungs; localized fibrinous pericarditis, and subendocardial ecchymosis.

Skin: The skin had a brownish tint and there was very marked pallor of the mucous membranes.

Heart: The heart weighed 350 gm. There was a moderate dilatation of the chambers. The epicardial surface of the right auricle presented a large area of ecchymosis. The musculature was flabby, and a pale brownish yellow. There was tigering of the papillary muscles on both sides. The valves showed no abnormalities except for several fine filiform gray vegetations on the posterior aortic cusp. There was diffuse ecchymosis beneath the endocardium in the right auricle. The coronaries were soft and patent throughout and free of atheromatous change.

Lungs: The lungs were edematous. The pleura over the right lower lobe presented a dull fibrinous exudate.

Liver: The liver weighed 1600 gm. It was soft and flabby in consistency. Cut surface was brownish in color and the lobules were indistinct. Scattered throughout the liver was seen an occasional pin-head sized, grayish dot.

Spleen: The spleen weighed 110 gm. It was very soft and flabby. Its cut surface was brick red in color and there were numerous small petechial hemorrhages within the pulp. The corpuscles were not clearly visible. The pulp was mushy in consistency and scraped away readily on the knife.

Kidneys: The kidneys together weighed 220 gm. and each measured 10 by 6 by 3 cm. The capsule stripped readily. The cortical surface was extremely pale and had a yellowish color. The stellate veins were prominent. The organs were extremely soft and flabby and the cut surface was very pale. The cortex was everywhere narrow and varied from 2 to 4 mm. in thickness. The medulla measured 15 mm. in thickness and was differentiated from the cortex with difficulty. The cortical markings were almost completely obscured. Pelves and ureters showed no abnormalities.

Bones: The ribs were extremely brittle, moderate pressure from without causing fracture of most of them. In places they presented fusiform swellings. In these areas, the cortex was reduced to a thin shell and was readily broken. The underlying marrow was grayish red in color, somewhat firmer than normal and rubbery in consistency. The medullary tissue in the lumbar vertebrae was irregularly grayish red in color and presented moderately firm grayish areas similar to those in the ribs. The medullary tissue in the shaft of the right femur likewise contained firm rubbery grayish pink tissue. The cortex, however, was of the usual thickness.

Microscopic Examination

Heart: In the heart there are areas of atrophy. Many of the fibers contain fine fat droplets which stand out readily when stained with Sudan III.

Liver: There is slight central fibrosis of the lobules of the liver and brownish pigmentation about the nuclei of the cells. Many of the sinusoids contain large vesicular cells similar to those seen in the section of bone marrow.

Spleen: The follicles of the spleen are few and small. There are large amounts of blood pigment throughout the pulp, some free in the interstitial tissue and some in the endothelial cells. In the sinuses of the pulp are seen many cells of the type described in the bone marrow. A moderate amount of congestion is present.

Kidneys: The glomeruli of the kidneys are for the most part intact. Some, however, show thickening and dilatation of the capillary loops and a diminution in the number of endothelial elements. In some places they are somewhat smaller than normal. The convoluted and collecting tubules show considerable change. In the cortex the tubules are dilated and filled with light pink-staining material (Fig. 1). In the medulla the tubules show extensive degenerative changes. In many places the epithelium is desquamated. The nuclear elements are faintly staining. The interstitial tissue is markedly increased. There are areas where the tubular elements are completely destroyed and replaced by a few scattered cells, apparently remnants of tubules and hyalinized edematous connective tissue (Fig. 3). Everywhere the tubules that are intact contain pink-staining material. In a few areas in the medulla the tubules

contain calcified masses (Fig. 2), and occasionally one finds in the lumen of some of the tubules some lamellated pink-staining material resembling concretions. The interstitial tissue throughout appears to be very cellular. On closer observation the cellular appearance is due to an increase in connective tissue elements although in some areas there are collections of lymphocytes. There is evidence of slight arteriolosclerosis with thickening of the smaller vessels and connective tissue replacement of an occasional glomerulus. The chief lesion seems to have affected the tubular elements of the kidney and apparently is a very severe nephrosis.

Fat stain shows a considerable number of fine fat droplets in the epithelium of the convoluted and collecting tubules.

Bone Marrow: The bone marrow from the femur shows extensive hemorrhage. The normal bone marrow tissue is replaced by large masses of densely packed cells. These cells are round, polygonal and oval in shape. The cytoplasm for the most part is indistinct. The nuclei are large, round and vesicular. Some are slightly compressed and spindle-shaped. The chromatin network is prominent and many nuclei contain definite nucleoli. Some are small and pyknotic. The cytoplasm of these cells is somewhat pinker than that of the others. Occasionally large bone marrow giant cells are seen. In addition to these, occasional prominent multinuclear giant cells are seen with considerable pink-staining cytoplasm and three or four oval, prominent nuclei. The capillaries are engorged. Some of the tumor nodules appear to have an irregular fibrous tissue capsule about them but not completely encircling the nodules. The oxidase reaction is negative.

CASE 2.

Clinical History: H. S., age 71 years, was admitted to the medical service Aug. 11, 1929, complaining of pain in the lower spine, right shoulder, left chest, and inability to walk. Six months prior to admission, the patient was struck on the chest and developed a severe cough with bloody expectoration. On the following day he had severe pain in the lower spine and extremities and was forced to remain in bed for several weeks. The pain had persisted until the time of admission and during the last three days he had suffered knife-like localized constant pain in the shoulder and left chest. Polyuria and hesitancy were present for some weeks, though no dysuria. For several months he complained of weakness, dyspnea on slight exertion, orthopnea, cough and expectoration.

On examination he was pale and emaciated. His respirations were rapid. Over the right clavicle near the sternal border was a rather soft small protruding tender mass. His ribs were tender to percussion. A systolic murmur was heard

at the apex, but the heart was not enlarged. The blood pressure was 135/75. There was kyphosis of the dorsal, and part of the lumbar spine with tenderness over the lower vertebrae. X-ray of the skull showed numerous punched out areas of rarefaction. Areas of rarefaction were found in lumbar vertebrae, pelvic bones, upper halves of the femora, the ribs, clavicles, scapulae and upper halves of the humera. The red blood cell count was 1,220,000, hemoglobin 20 per cent, white blood cell 7,800. Blood urea 52.2, creatinin 5.1. Wassermann negative. The urine had a specific gravity of 1012, and contained large quantities of albumin but no Bence-Jones albumose. The sediment contained some pus cells but no casts. Five days after admission the patient died with signs of a terminal pneumonia.

Autopsy Report

Anatomical Diagnoses: The anatomical diagnoses were: Multiple myeloma involving the ribs, spine and innominate bones; chronic nephrosis with contraction of the kidneys; fatty metamorphosis of the heart; cholelithiasis; prostatic hypertrophy; dilatation and hypertrophy of the bladder; polyps of the colon.

The body was that of an emaciated elderly man with a peculiar waxy pallor of the skin and mucous membranes. The upper part of the chest was flattened. The lower part bulged anteriorly and laterally. The ribs were very brittle and fractured readily on pressure.

Heart: The heart weighed 230 gm. The myocardium was pale and flabby and small pin-head yellow patches were scattered throughout. The chambers were of normal size. The endocardium and valves showed no abnormalities.

Lungs: The pleura were smooth and glistening except for fibrous tags at the bases. The upper and middle lobes were soft and crepitant. Both lower lobes were firm, airless, and on section had a dark red meaty appearance. From the lower lobes, dirty red fluid could be expressed from the cut surface. Bronchial mucosa and vessels showed no abnormalities.

Gall Bladder: The gall bladder was thin-walled and contained numerous pyramidal facetted black and yellow stones. Stones were found in the hepatic and cystic ducts but the common duct was patent.

Spleen: The spleen weighed 210 gm. and measured 14 by 7 by 3 cm. It was large and soft and on section rust brown in color. The corpuscles were not seen. The trabeculae were thin and delicate. Pulp scraped with difficulty. No tumor nodules were present.

Kidneys: The kidneys were small. Each weighed 100 gm. They were soft and yellowish in color. The capsules stripped easily, leaving a smooth surface. On section, the normal architecture was obscured and the surface had a homogeneous waxy appearance. The cortex was markedly narrowed, measuring 3 mm. in its widest portion. The pelvis of one kidney showed numerous petechiae. Ureters were patent.

Intestines: There were two small polyps in the lower part of the descending colon.

Aorta: The aorta showed very few raised white and yellow circular and oval atheromatous plaques and no ulceration, calcification or thrombi.

Bones: Several ribs were removed. The cortex was thinned out in areas. The marrow showed numerous grayish pink meaty nodules. Portions of the bodies of the lower lumbar vertebrae and of the left innominate bone showed extensive replacement of marrow by similar tumor tissue. The intervertebral discs were intact. The long bones were not removed. The brain and cord were not removed. The other organs showed no abnormalities.

Microscopic Examination

Lungs: There is edema and some emphysema in the lungs.

Spleen: The spleen is moderately congested. Follicles are not very prominent. A large amount of brownish pigment is present in the pulp tissue, primarily in the endothelial cells lining the sinuses. The arterioles show considerable thickening of the media and intima.

Aorta: The aorta shows typical atherosclerotic changes of the intima with calcification in the media.

Prostate: The prostate shows a variation in size of the glandular elements with increase in their number.

Testes: The testes show a marked increase in the interstitial connective tissue with atrophy of some of the seminiferous tubules and practically complete absence of spermatogenesis and replacement of interstitial cells of Leydig with connective tissue.

Thyroid: In the thyroid there is very marked calcification of the media of the arteries. Some atrophic changes in the lobules with an increase in the interstitial connective tissue are present.

Bones: In a section of rib, the bone marrow to a large extent is replaced by a very cellular mass. These cells are small, uniform in

size, closely packed with round, somewhat vesicular nuclei and prominent nucleoli. Cytoplasm is slightly pink-staining and forms a syncytial mass with the surrounding cells.

Sections through the long bones show similar tumor masses in the bone marrow. In places the cells are polyhedral in shape. Mitotic figures are not prominent. In many of the cells the chromatin content is arranged about the periphery of the nucleus in cartwheel fashion. Apparently this appears to be a plasmocytoma.

Kidneys: The kidney has a very striking appearance (Figs. 4 and 5). There is an enormous increase in the interstitial connective tissue in the cortex, with marked destruction, atrophy and replacement of the tubular elements. The glomeruli show only an occasional atrophic change with hyalinization and thickening of Bowman's capsule. The glomeruli are otherwise intact. The capillaries of some of the tufts are congested. The tubules are strikingly atrophic and large areas are destroyed and replaced by what appears to be a densely cellular fibrous connective tissue. In addition there are small clumps of lymphocytes throughout the cortex. In areas the intact tubules are markedly dilated and filled with pink-staining material that has in places a lamellated structure. The central core is somewhat more pink-staining than the periphery. In the medulla many of the tubules show degenerative changes (Fig. 5). There is some increase in the interstitial tissue and many of the tubules are filled with pink-staining masses. Several of the tubules in the medulla contain masses of calcium in the lumina and in other places the lining epithelium contains calcium salts. The arterioles of the kidney show some thickening, and in areas, obliteration.

The picture in the kidney is that of very marked chronic nephrosis with extreme interstitial changes and shrinkage of the kidney. There is a concomitant arteriolosclerosis of mild degree. The glomeruli are only slightly affected. Calcification in some of the tubules of the medulla is present. The failure to find Bence-Jones protein in the urine is of no great significance as the patient was under observation for a week only, and it is well known that in the late stages of myeloma the Bence-Jones albumosuria may disappear.

Discussion

In both instances, a nephrosis complicated the multiple myeloma. The nephrosis was characterized clinically by the presence of large amounts of albumin and Bence-Jones albumose (in one instance) in the urine, with a low specific gravity, a low concentrating capacity, a rise in the non-protein nitrogen of blood and little edema. The severe secondary anemia is probably due to the bone marrow disease.

The changes in the kidneys in both instances reported were severe tubular destruction in the cortex and medulla with extensive replacement by connective tissue, interstitial lymphocytic infiltrations, casts in the intact dilated convoluted tubules of the cortex, and calcification of an occasional tubule in the medulla. The glomeruli showed slight hyalinization in some instances, but were for the most part anatomically intact. The picture was apparently that of a severe chronic nephrosis with evidence of secondary inflammation and fibrosis and contraction of the kidney. Since there is no certain microchemical method of detecting the presence of albumose in tissue sections, we were unable to determine whether the casts in the tubules contained albumose.

Frederich Müller [10] recommended the term nephrosis to indicate a primary degenerative disease of the tubules of the kidney. With the subsequent work of Aschoff [11] and Volhard [12] this disease entity was definitely separated from the so-called inflammatory diseases of the kidney. Etiologically true nephroses are produced experimentally in bichloride poisoning and in poisoning with chrome salts. Mild nephroses are observed in acute infectious diseases and occasionally in lues. The severest nephroses have been observed in patients in whom no etiological factor for the severe degenerative process could be determined.

In the idiopathic lipoid nephrosis there is no loss of the ability of the kidney to concentrate the urine in the tubules since these remain functionally active and the specific gravity is high. A large amount of protein is excreted in the urine, the globulin-albumin ratio of the serum is reversed and edema is prominent. Hypertension is absent and there is no rise in the non-protein nitrogen. The usual course is relatively acute and the kidney may recover anatomically. The chronic nephrosis of multiple myeloma differs from the idiopathic lipoid nephrosis first described by Müller, Volhard,

and Epstein [13] both clinically and pathologically. In multiple myeloma there is true renal insufficiency characterized by a rise in the non-protein nitrogen of the blood, an inability to concentrate the urine with a corresponding low specific gravity. A large amount of protein is excreted in the urine (albumosuria and albuminuria), and the globulin-albumin ratio of the serum is reversed. Edema and hypertension are absent. Anatomically the nephrosis of myeloma proceeds to the end-stage of marked contraction of the kidney, and this extensive destruction of the tubules with fibrosis accounts for these differences in the clinical picture. Since concentration of the urine is said to occur in the tubules and since the tubules are destroyed in large numbers, the concentrating power is necessarily diminished and the specific gravity is low. With the destruction of large numbers of renal elements in the end stage of the nephrosis, the kidney function is strikingly impaired and even uremic manifestations may appear.

What relation does the Bence-Jones protein bear to the changes in the structure and function of the kidney? Is it possible for this protein substance to pass out of the blood through the normal kidney or is a previous injury to the kidney a necessary antecedent? And what relation does the Bence-Jones albumosuria bear to the severe degenerative disease of the tubules?

Anatomical kidney changes associated with Bence-Jones albumosuria are mentioned in most instances where the kidney pathology has been described in the literature. Of thirty instances with kidney lesions, about 65 per cent report positive Bence-Jones albumosuria. In about 25 per cent, Bence-Jones protein was not tested for, and in 10 per cent, no Bence-Jones protein was present. Of thirty-six instances where the kidney was described, thirty or 83 per cent report kidney lesions. Of these instances, twenty-seven described changes which in part are those of arteriolosclerosis of the kidney. In eight instances calcification of the tubules was reported. In six instances, a nephrosis was observed. In three instances, the arteriolosclerotic changes were associated with nephrosis, and in three instances the arteriolosclerotic changes were associated with nephrosis and calcification. Of eight instances with no gross kidney lesions, three were said to have Bence-Jones albumosuria, but in these cases there was no mention of the microscopic examination of the kidney.

In a few instances, inflammatory lesions were noted in the kidney, but these were apparently complications such as pyelonephrosis or abscesses of the kidney. A true nephritis was described in only one instance, to the authors' knowledge. There can be no doubt that many of the instances described as chronic interstitial nephritis and arteriolosclerosis are cases of chronic nephrosis with contraction of the kidney. However, the presence of some degree of vascular disease of the kidney in most individuals over 55 years of age may have masked the nephrosis in such cases.

It is evident from this study that in almost every instance of multiple myeloma with Bence-Jones albumosuria there is present a disease of the kidneys which is obviously unrelated to the disease multiple myeloma *per se*, and unassociated with the nephrosis. The frequency of arteriolosclerosis of the kidney in the age group 50 to 70 years suggests that this lesion is a purely accidental finding.

Although it is possible that the Bence-Jones protein may pass through a normal kidney, proof of this fact cannot be obtained from the study of the pathology of the kidney in multiple myeloma. The evidence that Bence-Jones albumose can pass through a normal kidney is based on experiments in which Bence-Jones albumose was injected intravenously in rabbits and in dogs. It is well known that the injection of a foreign protein into an animal previously uninjected is followed by the appearance of that protein in the urine of the animal. It is argued by analogy that the Bence-Jones protein acts in the body as a foreign protein and is therefore eliminated in the normal kidney. Stokvis [14] induced kidney changes in dogs following the injection of Bence-Jones protein intravenously, and recovered the Bence-Jones albumose in the urine. Ellinger [15] was unable to confirm this finding. Von Decastello [16] found that a previous injury to the kidney was essential in permitting the appearance of Bence-Jones albumose in the urine in dogs injected with Bence-Jones albumose. Krauss [17] again succeeded in producing a nephrosis with Bence-Jones albumosuria in rabbits injected intravenously with Bence-Jones protein. However, he injected 1.25 gm. of Bence-Jones protein intravenously into himself, and was unable to recover Bence-Jones protein in the urine. When injected, however, into a patient with hemiplegia and evidence of arteriolosclerosis of the kidney, Bence-Jones protein was recovered in the urine. The experimental evidence does not permit the conclusion that Bence-

Jones protein can pass through the normal kidney in man. Though Bence-Jones protein may not ordinarily pass through the normal kidney, it is possible that the accumulation of large amounts of this substance in the blood of patients may produce functional injury to the kidney glomeruli and permit the excretion of the protein. On the other hand, since some arteriolosclerosis with glomerular injury is present in most individuals of the age group in which myeloma is found, it is possible that this degree of injury may be sufficient to allow of the excretion of Bence-Jones protein in the urine.

It is conceivable that the constant excretion of Bence-Jones albumose through a kidney previously injured, and its accumulation in the tubules, may be responsible for the subsequent nephrosis occurring in certain instances of multiple myeloma. It is possible that some other factor is responsible for both the nephrosis and the Bence-Jones albumosuria, and that some metabolic disturbance analogous to that occurring in true idiopathic nephrosis may be present in multiple myeloma.

Calcification observed in the kidney may be interpreted as part of the so-called metastatic deposits observed in diseases in which bone is extensively destroyed. Calcification of tissue in the kidney, the glandular mucosa of the stomach and the alveolar walls of the lungs was first noted by Bender [18] in an instance of myeloma, and subsequently by Tschistowitscht and Kolessnikoff,[19] by Froboese,[20] by Morse,[21] Thannhauser and Krauss [6] and by Charlton [22] and Kleine.[8] The calcification may be due to a general disturbance in calcium metabolism with hypercalcemia. However, the injury to the tubules probably predisposes to its deposition in the kidney. In one of the cases reported in our paper, there was a hypercalcemia.

Summary and Conclusions

Two instances of multiple myeloma with severe nephrosis and shrinkage of the kidney are reported. A review of the literature reveals several other similar instances. A study of the pathological changes of the kidneys in instances of multiple myeloma associated with Bence-Jones albumosuria is made. From this analysis it is concluded that the pathological changes found in the kidney of multiple myeloma consist of three distinct elements, no one of which is constantly present but all three of which may be present: (1) a

nephrosis specifically associated in some way with the Bence-Jones albumosuria and the myeloma; (2) arteriolosclerosis of the kidney, an independent vascular disease of the kidneys, present in a milder or severer form in almost every instance of multiple myeloma occurring in the age group 50 to 70 years, and (3) calcium deposits in the kidney tubules dependent on a destruction of bone and the release of large quantities of calcium in the blood.

Clinically the nephrosis differs from the idiopathic type in the absence of edema and in the increase in the concentration of nonprotein nitrogen in the serum, and an inability to concentrate urine with a consequently low specific gravity to the urine. Anatomically the nephrosis is severe and the kidneys contracted. The kidneys are small and pale with a smooth surface and markedly narrowed cortex. Microscopically there is extensive destruction of the tubules of the cortex and medulla with replacement by dense cellular fibrous tissue. Though there is some hyalinization of a few glomeruli, this lesion is apparently associated with a concomitant arteriolosclerosis, the primary lesion being the destruction of the tubules.

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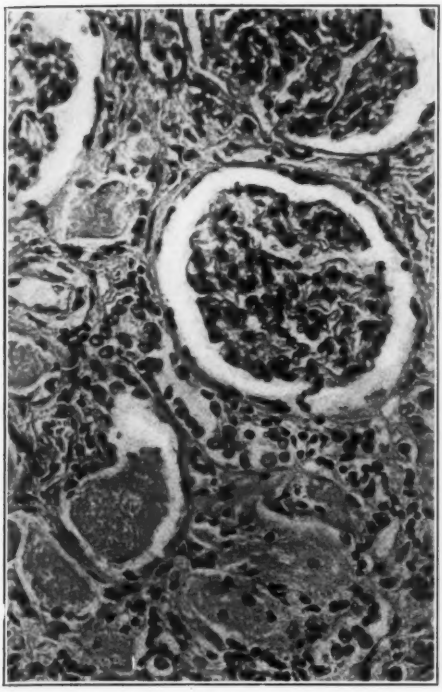
DESCRIPTION OF PLATES

PLATE 64

FIG. 1. Section through cortex of kidney of Case 1. Glomeruli intact, tubules dilated and filled with casts. Round cell infiltration of the interstitial tissue.

FIG. 2. Section through medulla of the kidney of Case 1, showing marked dilatation of the tubules with casts and calcification of one tubule.

FIG. 3. Section through medulla of kidney of Case 1. Extensive fibrosis with replacement of tubules. Round cell infiltration. Atrophy of remaining tubules.



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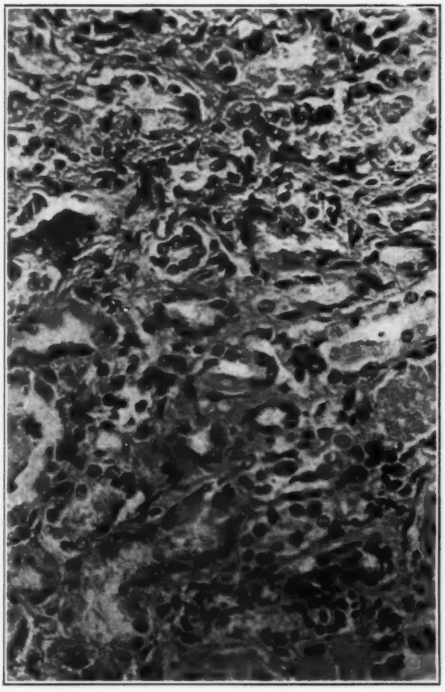

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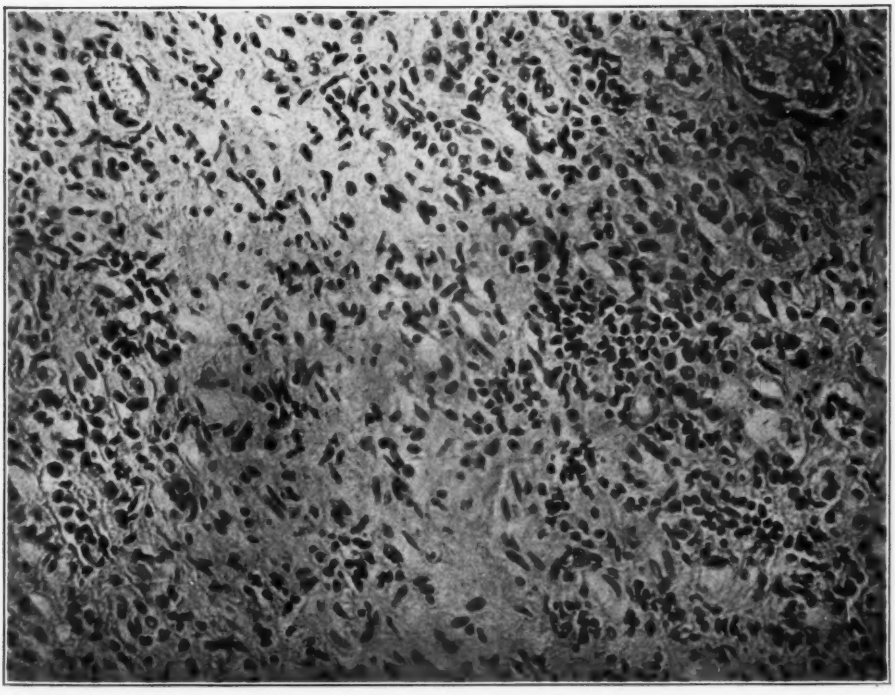


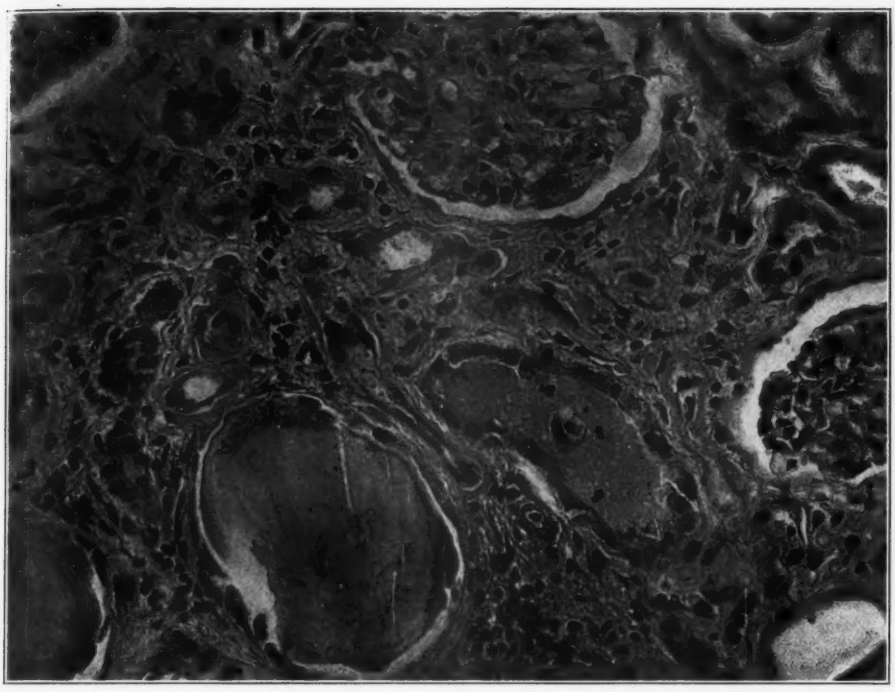
3

Perla and Hutner Nephrosis in Multiple Myeloma

PLATE 65

FIG. 4. Section through cortex of kidney of Case 2. Glomerulus shows slight atrophic change but is relatively intact. Marked dilatation of the convoluted tubules with flattening of the epithelium. The tubules are filled with casts.

FIG. 5. Section through medulla of kidney of Case 2, showing extensive fibrosis with destruction of tubules and round cell infiltration. Intact tubules are dilated and filled with casts.



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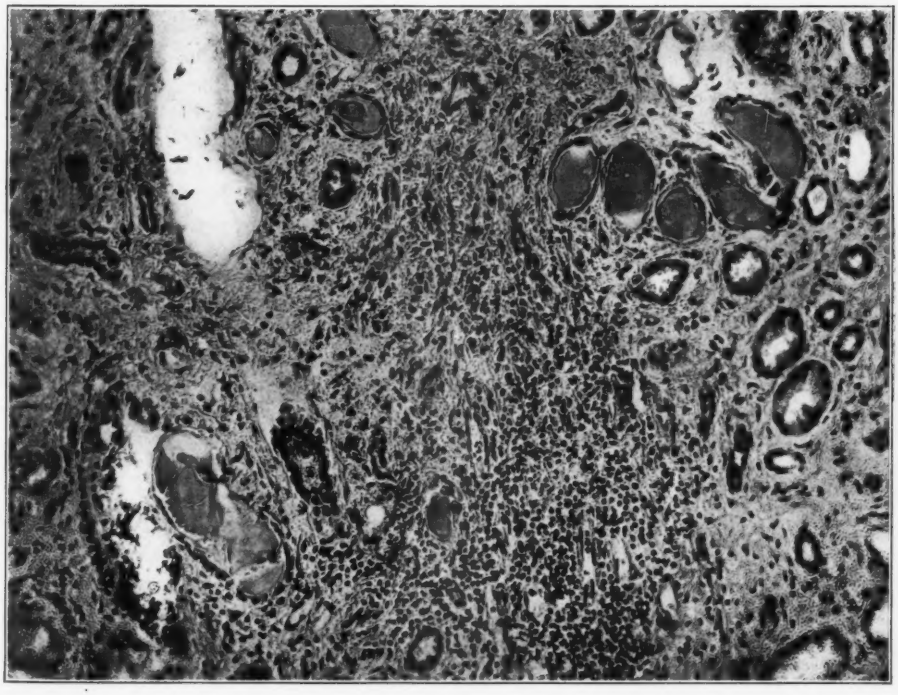

5

THE PATHOLOGICAL SIMILARITY OF THROMBO-ANGIITIS OBLITERANS AND ENDEMIC ERGOTISM*

JULIUS KAUNITZ, M.D.

Thrombo-angiitis obliterans and ergotism (gangrenous form) have many points in common. This is particularly true of their vasomotor, trophic and sensory symptoms and signs. Even though the histological descriptions in ergotism are meager, they show a resemblance in the important pathological characteristics; namely thrombosis with obliteration of the vessel lumina.

The cause of thrombo-angiitis obliterans is unknown, and if we are to consider ergot poisoning as the cause we must first know some facts about the probability.

It is well known that epidemics of ergotism were due to the eating of bread made of ergot-infected rye. These epidemics have been traced back as far as Galen, circa A.D. 200. For a complete history of epidemic ergotism up to 1888, the works of Krysinsky [1] and Allbutt and Dixon,[2] from whose works I have borrowed freely in this article, are recommended. There have been very few epidemics of any importance in the past 100 years because of the greater care, cultivation and separation of the ergot sclerotia from the rye grains. In spite of our knowledge and care there have been isolated epidemics as late as 1908. This is not at all surprising when we realize the quantity of grain that is known to be infected with the ergot fungus in our present day.

Since the ergot fungus attacks most of the grains and grasses, it is not strange that we have reports of its presence in most portions of the globe. As rye is the most susceptible host, it is natural to find this fungus most prolific in those regions where rye occurs in the greatest abundance. It has been reported to occur in every continent including Australia and New Zealand. In North America it has been found in Vermont, Connecticut, New York, Michigan, Tennessee, Indiana, Wisconsin, Minnesota, Iowa, Kansas, Wyoming, Montana and other states, besides various places in Canada.

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Atanasoff [3] says: "Grains, especially rye, in some seasons and in some fields are infected so heavily that nearly every head may have one or more sclerotia, as was reported from Wisconsin in 1917. Cases where 20 to 50 per cent of the heads were infected with ergot have been reported from various parts of the United States and Europe. The amount of ergot for 1917 in Connecticut ranged from 1 to 5 per cent. Decrease of the yield [of rye] by as high as 20 per cent has been reported from Russia." (As a result of ergot infection.)

The importance of the present-day ergot infection of rye can be judged by the defensive measures used by the grain farmers to remove the fungus. Many methods, such as sifting, screening, fanning and sedimentation are employed, all depending on the difference in size and weight of the grain compared to the fungus. It is considered that with careful cleaning of the seed the ergot can be diminished to from 0.06 to 0.17 per cent. It is of course not expected that such a diminution could occur where the ergot amounted to 5 or more per cent of the grain. From personal experience with twenty samples of rye flour obtained from grocers and the New York Produce Exchange in 1925, I found anywhere from five to twenty-five flecks of ergot on a microscopic slide. Considering the amount of ergot-infected rye bread consumed here and abroad it is surprising that cases of endemic ergotism are so rarely reported. It may well be that such conditions as thrombo-angiitis or Raynaud's and other vasomotor and trophic diseases have been overlooked as possibly being sequelae to ergot poisoning. This may be because of the mildness of the original intoxication and the insidious onset of the vascular changes.

In studying the nationalities and races affected with thrombo-angiitis obliterans, we find the disease most prevalent in people from those countries where rye bread is the staple article of diet, generally in the Northern Slavic countries — Russia, Poland, Ukraine, East Prussia and Lithuania. Most of the cases reported by Buerger [4] and Jablons [5] in New York City were immigrants from those countries. Buerger, who is responsible for much of the literature and experimental work on this disease and who has given it the name thrombo-angiitis obliterans, believes that the disease is peculiar to the Jewish race. In his large series of cases in New York City, patients were almost exclusively Jewish. Jablons reported

90 per cent Jews in a series of 200 cases in New York City. He mentions Idelson reporting 60 per cent Jews in a series of 226 cases from Poland, Lithuania and East Prussia. He quotes various other authors as reporting cases in Norwegian fishermen in Norway, Scandinavians in Minnesota, and Japanese and Chinese in their natural habitat. It would seem from this that thrombo-angiitis obliterans is more widespread than originally thought by Buerger. It is probable that the large percentage of cases reported in any particular race depends to a great extent on the character of the author's experience. In considering the susceptibility of the Jews to this disease, it is significant that this disease is very rare in the descendants of native Jews of the United States, England and Germany, whose dietetic habits are different from the Slavic Jews. It seems more rational to regard the susceptibility as one depending on habits and susceptibility peculiar to the individual, rather than to any racial idiosyncrasy.

Sex: Of 500 cases reported by Buerger three cases occurred in females. In Jablon's 200 cases, 1 per cent occurred in females. Idelson [6] reported 14 women in a series of 358 cases. The greater susceptibility of males to thrombo-angiitis obliterans is very evident from these figures. One can find a parallel here in the susceptibility to the gangrenous form of ergotism which affected the males to the greatest extent. In sixty-eight epidemics of ergotism, according to Krysinsky, the gangrenous form affected, with one exception, the males exclusively. The convulsive form affected the women, children and the aged. Renauldin [7] stated that the gangrenous form of ergotism does not affect females. Tessier [8] observed that spurred rye acts with less force on females. What is true of epidemic is also true of medicinal ergotism. In spite of the tremendous quantity of ergot consumed in this country [9] — 170,000 to 264,000 pounds imported yearly — one rarely ever hears of a case of gangrene in women. It is interesting to note that even in fowls we encounter an increased susceptibility in males. Gittinger and Munch [10] in an assay of ergot by the cock's comb method, found that the hens had no value, their combs showing slight blanching or no effect whatever; while, of the control, 90 per cent of the cocks gave satisfactory results.

It is not within the realms of this paper to consider why certain diseases are limited to one or the other sex. For our purpose it is

pertinent that both thrombo-angiitis obliterans and gangrene ergotism have a preference for the male sex.

Age: Thrombo-angiitis obliterans occurs most frequently in young and middle-aged men. In epidemic ergotism the gangrenous form, according to Krysinsky, occurred most frequently in young and middle-aged men.

Social Class: Thrombo-angiitis obliterans occurs principally amongst the laboring classes. This was also found true of epidemic ergotism. The explanation given is that rye bread, which was the cheapest form of food, was the principal article of their diet.

Diet: As the chief article of diet in the North Slavic countries is rye bread, it is most natural that the patients coming from those countries should admit eating rye bread. It is also natural for the poor laboring classes, who make up the largest proportion of thrombo-angiitis obliterans cases, to be big consumers of this cheapest form of food. Those patients whom I questioned, admitted eating large quantities. One-half to three-quarters of a pound of rye bread during a meal was not considered unusual. Rye bread as we know was also the universal diet of the patients afflicted with epidemic ergotism. Those who ate liberally of meat, milk and cheese suffered less severely, or not at all. The addition of meat and milk to the diet of people who consume large quantities of maize, serves to prevent the occurrence of pellagra. This additional diet may serve in a similar way to neutralize the toxins of ergot. Those people who eat much rye bread might be advised with profit to add meat and milk to their diets.

It is well known that large quantities of rye bread are consumed by the Germans, yet there are relatively few cases of thrombo-angiitis obliterans reported by them. It may be that they are more careful in selecting and cleaning their grain, or perhaps their more varied diet helps to prevent the disease. Another element to consider is the preparing of the bread. In the Slavic countries a sour bread is made of rye flour leavened with old rye dough instead of yeast. The dough is allowed to ripen each time for several days. It takes much longer than with yeast. A small quantity of dough is always saved for the next baking. It is possible that a rye flour rich in ergot might develop larger quantities of the so-called putrefactive substances such as histamin and tyramin if allowed to stand

for a long time. The Germans are not as partial as their Slavic neighbors to this sour rye bread.

To explain the occurrence of thrombo-angiitis obliterans in the Chinese and Japanese, from the standpoint of ergotism, one would have to know more about the diet of these people. It may be that their rice had been infected by ergot. In the more Northern districts where rice does not grow, rye bread forms a big part of their diet.

Symptoms

For the symptoms of gangrenous ergotism we are forced to rely on the reports of the epidemic form as the reports of the endemic form are practically limited to the medicinal intoxications. After the acute symptoms, such as headaches, vomiting, cramps, diarrhoea, etc., agonizing pains appear generally in the legs. These pains, which are said to penetrate the limbs like fire, both precede and accompany the gangrene. The limb becomes livid, which in some cases is preceded by an erysipelatous blush. The cyanosis passes into darkness and blackness, and finally gangrene, which may be either dry or moist, generally the former.

The artery is felt to tighten from day to day and the pulse becomes very small until finally it is imperceptible. Amongst the sensory symptoms mentioned are formication, anesthesia, coldness, heat and pain. Tonic contractions of the legs are also mentioned. There may be pallor, rubor, or cyanosis. Gangrene may follow months after the initial intoxication.

The chief symptoms of thrombo-angiitis obliterans are burning or cramp-like pains in the calf of the leg. There is generally present paresthesia, anesthesia, formication, coldness or heat. There may be pallor, cyanosis or rubor. When the affected leg is elevated it immediately becomes bloodless, but soon changes from pallor to the original redness or cyanosis when placed in the pendant position. There are trophic changes to be noticed in the skin and nails of the fingers or toes affected, to which may be added ulceration and gangrene. Occlusion of the artery is essential to the diagnosis of thrombo-angiitis obliterans. The symptoms occur in some cases long before the complete thrombotic occlusion. This is particularly true of the vasomotor and sensory symptoms and suggests the possibility of recurrent spastic contraction of the diseased vessels.

In comparing gangrene ergotism and thrombo-angiitis obliterans we note that we have in both, symptoms and signs of a vasomotor and trophic condition. We have in both conditions pallor, rubor and cyanosis; pains, paresthesias and contractions in the legs; imperceptible pulse, trophic changes, ulceration and gangrene.

It is interesting to note that the patients, outside their local symptoms, appear to be in splendid health in both these vascular diseases.

Course

The course of thrombo-angiitis obliterans is very chronic, lasting many years. It is not known how soon the intoxication occurs before the symptoms. In ergotism, symptoms of gangrene have been noticed to occur several months after the original intoxication. In horses, Buffum [11] noticed gangrene to occur two years after the initial ergot intoxication. If such late manifestations occur in humans it is not strange that the original intoxication is lost sight of. Such may also be a possibility in thrombo-angiitis obliterans. It is possible that susceptible individuals, by daily feeding with rye bread slightly infected with ergot, may not show acute manifestations of ergotism but later develop the chronic manifestations of thrombo-angiitis obliterans.

Pathology

Only some of the salient features of the pathology of thrombo-angiitis obliterans will be described here. For details on this subject, Buerger, Mahorner,[12] and Ramirez [13] are recommended.

The lesions of thrombo-angiitis obliterans are generally found in the extremities and occasionally in the viscera. They are in part due to neurotrophic disturbances, but principally to a vascular occlusion which leads to infarction. The typical lesions are found in the blood vessels, which become thickened and thrombosed with obliteration of their lumina. The veins are often the seat of acute thrombophlebitis. This acute venous inflammation and thrombosis has led Buerger to apply the name thrombo-angiitis obliterans to this disease. It was his opinion that the disease began with an acute inflammation and thrombosis of the vessel. Earlier authors, Friedländer,[14] and some of the more recent authors, Ramirez and Mahorner, believe that thrombosis is secondary to an intimal proliferation.

The latter believes that even the acute thrombophlebitis of this disease is a superimposed condition, other vascular changes having preceded it.

The theory of the gradual narrowing of the lumen by the encroaching thickening intima is more consonant with the gradual impairment of the circulation noticed in this disease. An acute inflammation accompanied by a sudden thrombosis in an artery would produce very acute local manifestations with gangrene at the outset of the disease before collateral circulation could be established.

It is a question whether it is wise to draw definite conclusions of the pathogenesis in the arteries from the findings in the acutely inflamed veins. Acute arterial inflammation is relatively rare, whereas acute phlebitis is common. This is not so surprising when we realize that the veins, particularly of the extremities, receive tribute directly from the superficial tissues, frequently the seat of infection.

Bacteria have frequently been found in thrombo-angiitis obliterans but none has so far been proved to be specific to this disease. In the absence of this evidence and the fact that the patients rarely have any of the constitutional symptoms of bacterial diseases, one should seriously consider as a cause an intoxicant capable of inducing the pathological changes of this disease.

In following the pathological progress in the vessels one might suggest that an initial intoxication, by injury or only severe excitation, results first in a contraction of the walls and in intimal hyperplasia (Fig. 1). The second phase is the clot which becomes attached to the intimal process. Both this intimal process and the red clot undergo organization and often fuse so thoroughly as to make one fibrous mass. One is then unable to identify with any certainty what is intima, thrombus, or both (Fig. 2).

As organization takes place, various areas of the vessel would become impoverished unless some compensatory circulation were established. Small vessels are formed in the fibrotic mass and media to offset the impaired circulation. These new vessels are not found in the adventitia which perhaps has an independent circulation. These new vessels are one of the characteristics of the later phases of the disease.

Arteries are frequently found with their accompanying veins and nerves adherent to the adjacent structures. These nerves are fre-

quently found to be denser on account of the increased connective tissue. Many of the nerves are found in a state of degeneration. This is attributed to the ischemia and not correlated with any cerebrospinal changes. Whether the cerebrospinal tract is affected by this disease is not known as no autopsy report of its investigation exists.

Pathology of Ergotism

We have unfortunately very meager information of the pathology of ergotism. We are familiar with the text-book's description of a contraction and thickening of the vessel wall and a thrombosis of the lumen followed by gangrene of the extremity. Dr. Mitchell Bruce [15] says that the posterior columns of the cord show sclerosis. In the constricted and thrombosed arterioles a glutinous matter is found and the vessels either primarily or secondarily undergo hyaline degeneration, especially of the tunica intima.

As in thrombo-angiitis obliterans, the visceral vessels may also be affected. Perhaps the most detailed pathological report on ergotism in humans is the one by Vinogradoff [16] on the epidemic of acute convulsant ergotism that occurred at Viatka in 1889. Only the viscera were found affected, principally the liver, kidneys and spleen. Nearly all the large vessels of these organs contained thrombi. Some were red, others contained fibrin with scattered erythrocytes. In smaller branches of the portal vein organized thrombi were found. Some vessel walls were thickened, their lumina narrowed to such an extent as not to permit more than two or three erythrocytes to pass. Marked intimal proliferation was observed in some vessels. Many of the vessels had undergone fibrosis or hyaline degeneration. In spite of the more acute lesions described in these cases of ergotism, it is possible to correlate some of the vascular changes with those occurring in thrombo-angiitis obliterans.

As I could not obtain pathological sections of chronic ergotism for my studies, I attempted to produce this condition in animals. In my early experiments I employed the usual laboratory animals: mice, guinea pigs and rabbits. I found these rodents very resistant to ergot and had to change to roosters, which have long been known to develop gangrene of the comb after the ingestion or inoculation of toxic doses of ergot.

Some of the pathological data of three ergotized roosters will be

described here. The first one, although not of chronic ergotism, is described to illustrate how acute a process may be as a result of a change in the vascular tone, and also on account of its possible bearing on the acute lesions of thrombo-angiitis obliterans where no bacteria have been found. Complete protocols will be published elsewhere.

Experiments

Cock No. 24: Hybrid, red and white leghorn cock about 7 months old, weight 1250 gm., fed 28 gm. powdered Russian ergot in four days. Died of exhaustion on the ninth day after the initial feeding.

Autopsy: The animal appears emaciated, weight 880 gm.; the comb is very dark purple, the posterior tip is dry, hard and black (dry gangrene). There is a line of demarcation about 1 cm. from the tip. The border of the wattles, the breast and the rump is discolored with a dark hemorrhagic rash. On section of the skin the purpuric rash is seen to extend through to the pectoral muscles and into them. There is very little subcutaneous or omental fat. Heart normal; lungs normal, except for a small area of reddish consolidation at the left base; liver has a grayish infarct about 5 cm. in circumference.

Gross Pathology: Gangrene of the comb; purpura of comb, wattles, skin of pectoral and rump regions; consolidation of the base of the left lung; infarct of the liver.

Microscopic Examination: Lesions of acute ergotism found in sections of the base of the posterior portion of the cock's comb.

Section A. The larger arteries are somewhat contracted; the intima is puckered up. There are some spaces (fat globules) in the intima and subintimal regions. The intima stains in a somewhat hyaloid manner and has some vacuoles in its midst (Fig. 3).

Section B. About the middle of the posterior portion of the same comb. The central stalk shows very marked hyperemia. The larger vessels are engorged; many small vessels are visible which are not present in the preceding section. The arteries are dilated, their coats stretched thin. There is no evidence of endarteritis nor of any lesion of the media.

Section C. Near the tip of the posterior portion of the comb, proximal to the line of demarcation (Fig. 4). The central vascular stalk shows condensation of the fibrous fatty tissue. The vessels are

engorged with old blood. There is evidence of marked stasis. On either side of the vascular stalk there is condensation of the mucoid tissue with a disappearance of the nuclear elements: this condensed tissue stains quite blue with the hematoxylin and eosin stain.

The erectile tissue in the periphery of the mucoid tissue and just under the epithelium is greatly in evidence. There are more blood spaces and there is more engorgement. The papillae of the epithelial covering are flattened by this engorgement. There is some edema in the epithelium and the epidermal layers are increased.

Section D. Area of dry gangrene; tip of posterior portion of the comb, distal to the line of demarcation. The stalk area is composed of condensed mucoid tissue, the nuclei of which are in a good state of preservation. The vessels in the stalk are markedly engorged with blood. The erectile tissue around the stalk is very much in evidence, the blood spaces being markedly engorged with blood. In some of these spaces are to be found black amorphous masses, which are evidently degenerated blood pigment. In some portions there is early vacuolization in the subepidermal layers of the squamous epithelium. It would seem that this picture suggests attrition of tissue, and early stage of dry gangrene.

A similar picture is present microscopically in the section proximal to this, in which the gross picture is not yet that of necrosis. This description coincides with the gross pathology, which suggests a pregangrenous condition.

Cock No. 25: White leghorn cock about 1 year old, weight 500 gm. This case is of a more chronic duration, about seven months, the animal having been fed 180 gm. of ergot intermittently for four months. It developed vasomotor and trophic disturbances of the comb two months after the initial feeding.

Autopsy: The only gross lesion to be found is in the comb which is about twice its natural thickness. It is purple at its tip and pale at the base. Its entire surface is covered with small dry grayish scales and numerous fine capillary hemorrhages.

Pathological Histology: Section through the middle of the posterior portion of the comb. There is no change in the vascular stalk. Some of the arteries show vacuolization in the adventitia. Some of these vacuoles are large and lined with endothelioid cells; some of these are found throughout the vascular stalk. They suggest chronic lymphedema. One of these vessels shows marked intimal

thickening with great vacuolization of the pathological endothelium, which is irregularly heaped up to many layers in all but one small sector.

Microscopic Examination: The mucoid layer is markedly thickened: the fibrillae are greatly separated and their nuclei are few in number. This is all suggestive of chronic edema. A great many cells of the midlayers of the dermis show marked vacuolization, the nuclei standing out in the periphery of these spaces. This suggests chronic lymphedema. The epidermis appears more granular than usual, and is separated from the dermis by a distinct layer containing spaces (Fig. 5).

This animal developed vasomotor and trophic changes in the comb without having developed acute symptoms. Some of the vessels showed chronic endarterial changes with narrowing of the lumina. The marked stasis, edema, etc., could not be accounted for by the findings in these vessels which were not actually occluded. We can only deduce that these vessels which were in a state of spasm as a result of ergot feeding continued in this spastic state for three months after this drug was discontinued.

Cock No. 23: Plymouth Rock about 15 months old. This case is that of a rooster which was fed about 250 gm. of ergot over a period of one year. He was fed large doses in the seventh month and developed very acute symptoms such as weakness, dyspnoea, diarrhoea, etc. There was a necrotic process on the middle tip of the comb, the latter being purplish in color. An ulceration appeared at the base of the neck in front, which was found to communicate with the gullet from where much of the food was expelled. This fistulous tract was closed up with sutures and ergot was fed to him again until the fistula reopened about five months later.

As we are primarily interested in the affected vessels and the tissues they supply, only the comb will be considered in the autopsy of this animal.

Autopsy: The comb is slightly swollen, dry and rough. It is contracted to one side and has a nodule firm to the touch, 3 mm. in diameter, at its junction with the beak.

Pathological Histology: The central stalk shows one of the arteries supplying the surface of the comb to be the seat of marked change. There is an extensive heaping up of the intima which is markedly vacuolized, giving the appearance of fatty deposits. There is a

distinct thrombus which is apparently firmly attached to one side of the intimal ring and apparently in a stage of organization. The media and adventitia are comparatively uninvolved. This lesion has all the apparent marks of the condition called thrombo-angiitis (Fig. 6).

Microscopic Examination: Several other arteries of the vascular stalk are found to have the same intimal lesions, but in none of these are there attached organizing thrombi (Fig. 7.). These latter correspond to endarteritic lesions. The mucoid tissue is unchanged except toward the epithelium where it is condensed. Here the erectile tissue shows some diminution in the size of the blood spaces. The squamous epithelium is somewhat condensed and the epidermis is in greater evidence.

It might be argued that the chronic endarterial changes in this animal resulted from the injury caused by acute ergotism. In the preceding animal, however, marked intimal proliferation occurred as a result of chronic intoxication. It may be that chronic changes occur as a result of either acute or chronic ergot intoxication, very much as in bacterial intoxications.

If we were to consider some of the essential pathological changes found in both human and experimental ergotism, such as thickening of the vessel, particularly the intima, and the thrombus formation with organization, we might argue the identity of ergotism with thrombo-angiitis obliterans. Complete occlusion with canalization of the thrombus which was absent in ergotism might occur in cases of longer standing. Several years are perhaps necessary to develop this chronic process. An acute condition superimposed on a chronic one may be due in ergotism and thrombo-angiitis obliterans to a reintoxication with the causative toxins.

Toxicology

Ergot, *Claviceps Purpura*, is a fungus that attacks most of the grains and many of the grasses, but its most common host is rye. The fungus quite early in the life of the rye plant incorporates itself into the rye heads and becomes a part of certain of the grains. The vicarious grains appear somewhat larger than the normal grains on the same head, besides being considerably darker than, and easily distinguished from, the rye grains. These abnormal grains are

known as sclerotia and are a stage of the life cycle of the ergot fungus.

The growth and abundance of the ergot sclerotia is dependent to a large extent on moisture. The epidemics were observed by many authors to occur after a damp spring. It is probable also that the dampness may also influence the quantity and type of toxin elaborated by the fungus, for it has been noticed that in certain regions and at certain periods the gangrenous form of ergotism predominated, while in others the convulsive form was in greatest evidence.

Ergot is not the simple substance it was originally thought to be. Even today the pharmacologists are not quite agreed upon the active principals of this drug. Briefly it may be stated that in addition to its chief active substances, ergotamin and ergotoxin, there are found relatively small quantities of so-called putrefactive substances, histamin, tyramin and cholin bodies. The action of ergotamin and ergotoxin can best be described as inhibitors of the motor sympathetic fibers. This is best proved in their counteracting the glycemic and pressor action of adrenalin. Contrary to the accepted belief, ergotamin does not constrict the blood vessels. This phenomenon is most likely due to the other substances in ergot, histamin and tyramin. Tyramin is a very powerful arterial constrictor, whereas histamin, although it has slight arterial constricting qualities, is chiefly a capillary dilator. The combination of these three substances, ergotamin, histamin, and tyramin, undoubtedly favors the production of gangrene. Tyramin by constricting the arteries, and ergotamin and histamin by dilating the capillaries cause a marked stasis which eventually leads to gangrene.

Both tyramin and histamin produce uterine contractions. The latter in dilution of one to a hundred million produces vigorous contractions of the frog's uterus. Histamin when injected in a cock intramuscularly will cause a very prompt darkening of the comb. This phenomenon is much more vigorous and quicker than when whole ergot is employed. It appears from this that the present cock's comb method of assaying ergot in this country is faulty, since it does not distinguish between its principal alkaloids and one of its so-called impurities — histamin.

The action of whole ergot takes place perhaps through the central nervous system, and, to some extent, local stimulation. Although Albutt and Dixon did not succeed in diminishing the caliber of ves-

sels by perfusing them with ergot, such effects have been obtained by perfusion with histamin.[17]

The motor effects of ergot are of two types, a chronic contraction of the uterus and in the skeletal muscles (epidemic convulsive ergotism), and a tonic contraction such as occurs in the vascular muscles leading to gangrene. These two different motor effects may be due to the individual substances present in ergot, such as ergotamin, tyramin or histamin, which account for the variation in the types of epidemics, the gangrenous or the convulsive form of ergotism predominating depending on the predominant toxin.

Albutt and Dixon ascribe the possible differences in the strength and action of the various ergots to the ground on which they grow. They compare ergot in this respect with *Papaver somniferum* in that the same opium grown in Turkey has a richer yield in morphin than when grown in England. It is quite possible that certain yields of ergot also contain more or less histamin and tyramin depending on the country where they were grown. In the foregoing experiments, I obtained my best results with Russian ergot. The relative content of ergotamin, histamin and tyramin in the ergot of this country, Russia, Poland and Spain may prove of interest and importance.

The seasons and the "freshness" of the ergot also deserve consideration. The Abbé Tessier,[18] commenting on the conditions likely to promote an epidemic of ergotism, said "that the district was damp, that the vegetable products were ill thriven and stunted, that the inhabitants were in bad health, being reduced by want and malaria." Salerne [19] proved with experiments in animals that fresh ergot, which was most toxic, lost its toxicity in a few months.

Guggisberg [20] maintains that both histamin and tyramin occur only in old ergot and are not found in perceptible quantities in fresh ergot.

As has been mentioned, a sour rye bread is made in which the dough is allowed to leaven for several days, without yeast. Whether the ergot present might elaborate in this dough increasing quantities of histamin and tyramin or cholin bodies, and so become more toxic is a matter of importance and should be determined.

We have considered how ergotamin, histamin and tyramin, by a combination of arterial constriction and capillary dilatation and stasis, lead to acute gangrene. The angiospasm which induces

trophic changes also accounts for such phenomena as intermittent claudication, local syncope and asphyxia, cramping pains in the legs, etc., as occur in arteriosclerosis, Raynaud's disease, thrombo-angiitis obliterans and ergotism.

As has been suggested, the acute reactions that recur in the vessels of thrombo-angiitis obliterans may be due to an allergic response to ergot. If this suggestion is to be given consideration, then histamin, one of ergot's principal ingredients, should first be thought of because it is already looked upon with suspicion as the biochemical culprit of anaphylaxis.

Conclusions

There is much evidence in favor of an identity of thrombo-angiitis obliterans and ergotism. There are also some dissimilarities, but they can be ascribed to a difference in chronicity.

Ergotism should be produced in animals, preferably mammals, with a view to obtaining a chronic process of at least several years duration, for comparison with thrombo-angiitis obliterans, Raynaud's disease, erythromelalgia, sclerodactyl, etc. The results obtained in roosters, although suggestive, are too far removed biologically for definite comparison.

Careful investigation should be made of the cerebrospinal tract in all these vasomotor and trophic diseases. The cord has been neglected in the study of thrombo-angiitis obliterans.

A study should be made of the difference in the histamin and tyramin content in addition to the ergotamin in the ergot from various countries. Such studies should also be made of rye breads leavened in the ordinary way with yeast, and with old dough. Studies should be made with these ergot substances alone, and in various combinations on the effect on the vessels. Studies should be made with these substances from the allergic standpoint on the vessels, particularly histamin, which is a suspected substance in anaphylaxis.

It is hoped that these studies will lead to the prevention of some vasomotor and trophic diseases whose origin is not known.

SUMMARY

We have shown:

1. That both thrombo-angiitis obliterans and ergotism (gangrenous form) occur most frequently in people of the same sex, age and social status.

2. That the symptoms and physical signs may be the same in both conditions.

3. That the pathological findings in both may be the same in the earlier stages.

4. That the main article of diet in both conditions is rye bread.

5. That ergot is a common infection of all grains, particularly rye, in every continent of the globe.

NOTE: I wish to acknowledge my obligation to Dr. Irving Simon for the microscopic descriptions, and to Dr. A. A. Eisenberg for the facilities of the pathological department of the Sydenham Hospital.

Grateful acknowledgement is also made to Mr. and Mrs. Herbert M. Rothschild for their splendid coöperation.

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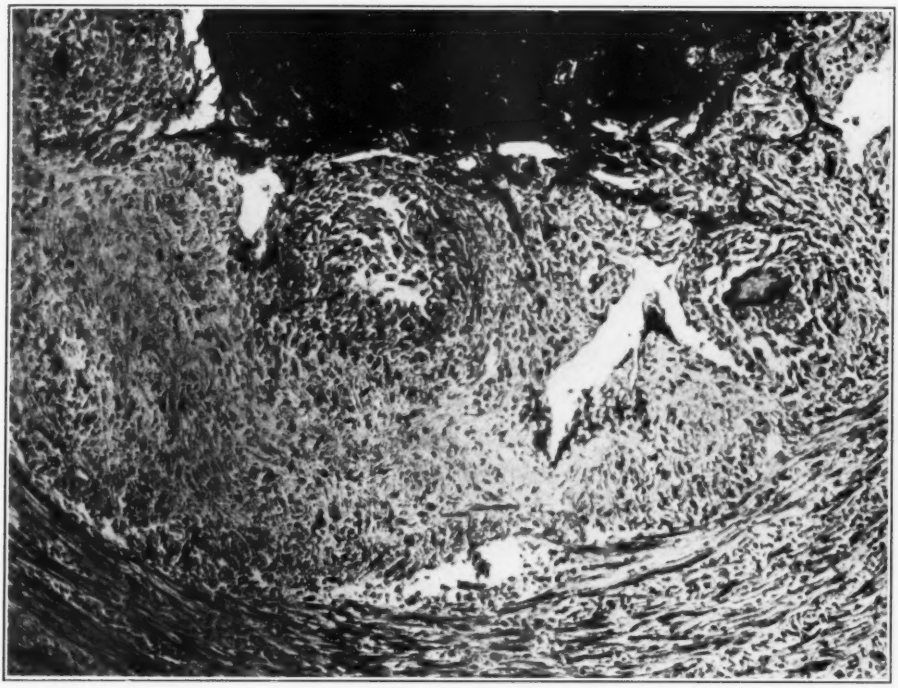
DESCRIPTION OF PLATES

PLATE 66

FIG. 1. Early stage of thrombo-angiitis obliterans, showing marked hyperplasia of the intima, to which is attached a recent thrombus. Note the invasion of the thrombus by the intimal cells. This will result in a fusion of the thrombus with the hyperplastic intima.

FIG. 2. Thrombo-angiitis obliterans in three vessels illustrating three later stages. To the right a vessel is shown to which a thrombus has very likely been attached to the hyperplastic intima, with which it became fused and organized so that there is now no means of identifying the two processes. To the left is a vessel in which the hyperplastic intima is the important feature. The vessel in the middle illustrates the end process of thrombo-angiitis obliterans.



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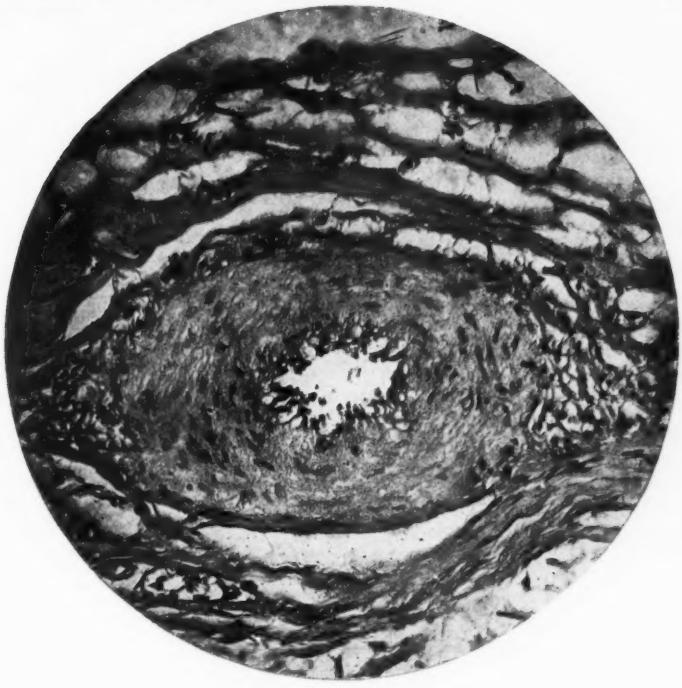
Kaunitz Thrombo-Angiitis Obliterans and Endemic Ergotism

Plate 67

Fig. 3. Acute ergotism in an artery at the base of the posterior portion of the cock's comb showing marked thickening of the vessel and contraction of the lumen. The muscularis appears edematous and stains poorly.

Fig. 4. Acute ergotism of the cock's comb near the posterior tip showing marked dilatation of the vessels and stagnation of all the tissues with old blood.



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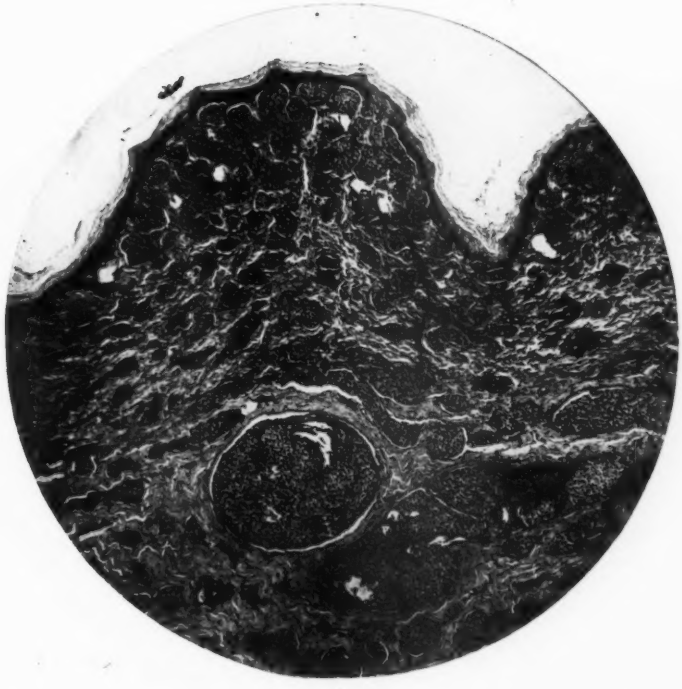

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PLATE 68

FIG. 5. Chronic ergotism of the cock's comb showing edema of the epithelial layer and desquamation of the thickened epidermis.

FIG. 6. Chronic ergotism in a vessel of the cock's comb showing marked intimal hyperplasia with an adherent thrombus which is fused and organized.

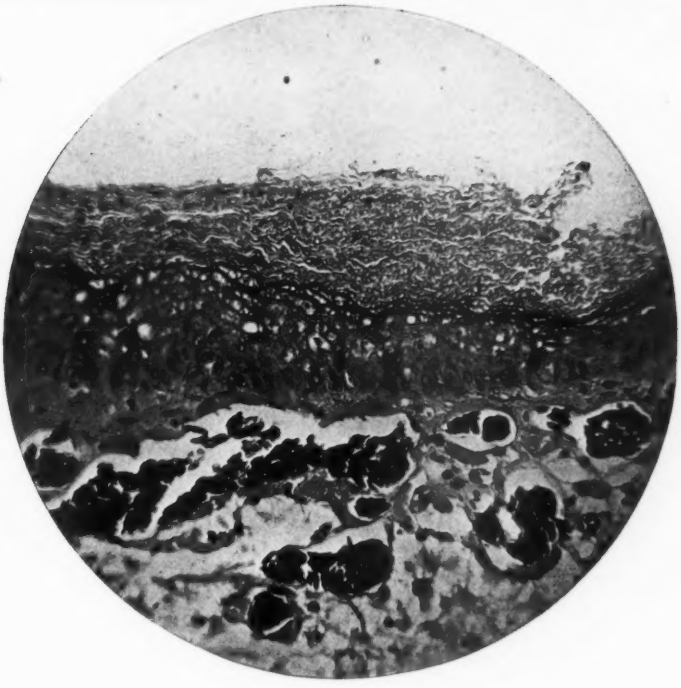

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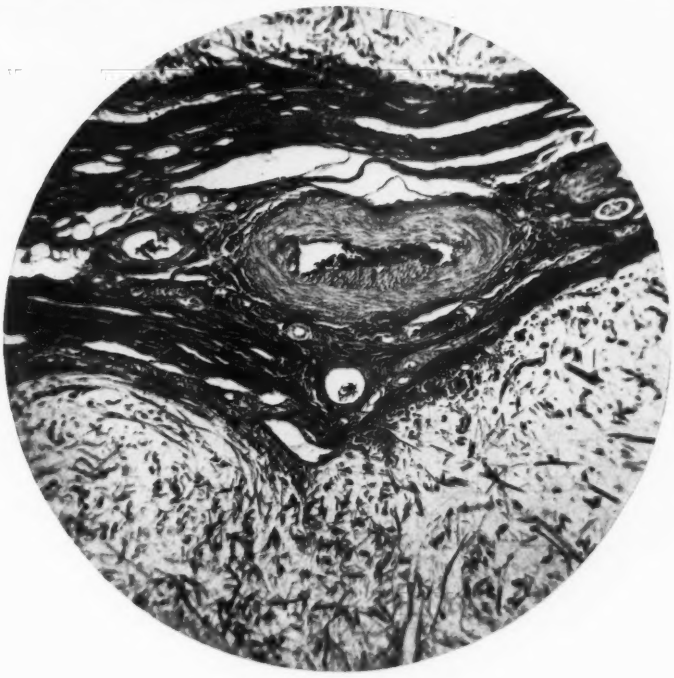
PLATE 69

FIG. 7. Chronic ergotism, cock's comb. Marked proliferation of the intima in an artery of the median stalk. Hematoxylin and eosin stain. × 50.

FIG. 8. Transverse section of a normal cock's comb. (1) Median vascular stalk. (2) Mucoid area. (3) Vascular erectile tissue. (4) Epithelial covering. Hematoxylin and eosin stain. × 10.



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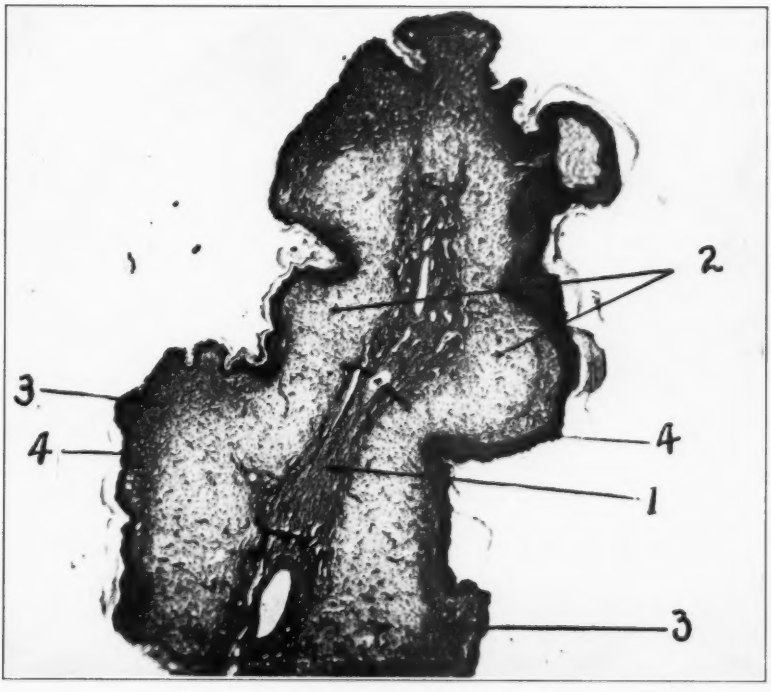

8

A CONGENITAL ANOMALY OF THE HEART (TRUNCUS ARTERIOSUS COMMUNIS WITH SUBACUTE ENDOCARDITIS) *

KNOX H. FINLEY

(From the Department of Pathology, Yale University School of Medicine, New Haven, Conn.)

INTRODUCTION

Truncus arteriosus communis is one of the rare types of cardiac malformation. Abbott,[1] in a recent article, reports twenty-three cases of this anomaly from the literature and other sources. One case has since been reported from this laboratory by Zimmerman.[2] The embryological factors responsible for this abnormality are discussed in detail by Abbott and Shanly.[3]

An individual with truncus arteriosus communis seldom lives beyond the period of childhood and rarely develops an intercurrent infection of the heart. Lesions similar to those found in this case are therefore unusual. It is well known, however, that intercurrent cardiac infections are common in many other types of congenital heart diseases. The case here reported is of special interest because of the valve injuries, the age of the patient and a ten-year period of observation in the medical dispensary and ward services.

REPORT OF CASE

Clinical History: The patient, a female, was under observation at the New Haven Hospital and Dispensary for a period of ten years prior to her death at 22 years of age. In 1919, the patient, then 12 years of age, reported to the dispensary complaining of nervousness and palpitation. She was born a "blue baby," was always cyanotic and physically could not exert herself beyond such moderate exercise as walking. Physical examination revealed cyanosis and malnourishment. The cyanosis was general over the face, hands and feet. The finger tips were markedly clubbed. The left border of cardiac dullness extended out to the anterior axillary line and the apex impulse was felt 11 cm. from the midsternal line.

* Received for publication December 19, 1929.

Presystolic and systolic thrills were felt over the apex and at the left sternal border at the level of the third and fourth costal cartilages. The heart sounds were regular and the rate 60 beats per minute. The first apical and second pulmonic sounds were accentuated. Along the left sternal border, high pitched diastolic and systolic murmurs were audible. The blood pressure systolic-diastolic was 90/60 mm. Hg.

The monthly dispensary visits of the patient until her first entrance to the hospital revealed no changes in her condition. In 1923, at 17 years of age, she was admitted to the hospital for the first time complaining of shortness of breath on the slightest exertion. Physical examination disclosed cyanosis and malnourishment, with clubbing of the fingers and toes. Additional signs in the heart were systolic and rumbling diastolic murmurs at the apex. During her five weeks' hospitalization the cyanosis decreased but never entirely disappeared. The clinical diagnoses at this time were: (1) congenital heart disease, patency of interventricular septum, and (2) rheumatic heart disease, with mitral stenosis and insufficiency.

Following her discharge, the patient continued to make frequent visits to the dispensary. Her only new complaints were occasional precordial pain and swelling of the ankles.

In May 1929, at 22 years of age, and one month prior to her second entrance to the hospital, she felt a localized sharp epigastric pain of ten minutes duration. One week later an upper respiratory infection developed and was accompanied by considerable coughing without sputum. She entered the hospital, complaining of a cold and chills. The teeth contained many fillings and several cavities. The tonsils were greatly enlarged and a thick yellow mucoid material covered the posterior pharyngeal wall. The signs in the heart were unchanged except for a blowing systolic murmur heard over the pulmonic area. The infection abated and she was discharged in three days.

Two months later for the third time she reported to the hospital because of chills and joint pains which had begun ten days before. The pain was most marked in the left knee-joint and there was also swelling of the left ankle. The patient, as previously noted, was malnourished and cyanotic and further appeared acutely ill. The signs in the heart, found on previous admissions, were unchanged

except for an additional long, blowing diastolic murmur over the pulmonic area. The temperature was 104.5° F, the pulse 135 per minute and the respirations 25 per minute. The blood pressure was 80/50 mm. Hg. On July 7th, the fourth day after admission, the spleen was palpable on deep inspiration. Blood cultures taken on three different occasions showed heavy growths of *Streptococcus viridans*. On July 26, three weeks from the date of hospital entrance, the patient complained of pain and numbness in the left leg and was unable to move her toes. Pulsation of the arteries of this extremity could not be felt. Cyanosis of the left leg rapidly increased. On July 28th, she became delirious and stuporous; the temperature rose to 106° F, the respirations became rapid, and the patient died on the afternoon of the same day.

The laboratory findings were: red blood cells 6,500,000 (the red blood count was found constantly high on all three hospital admissions), hemoglobin 120 (S), white blood cells 26,000 with 84 per cent polymorphonuclears and 13 per cent lymphocytes. The urine contained a heavy trace of albumin with 9 to 12 white blood cells per high power field. Electrocardiogram showed normal sinus mechanism with an average rate of 100 per minute (Chart 1). The chief ventricular deflections were downward in Lead 1 and upward in Lead 3. The auricular waves in Leads 2 and 3 were quite large and pointed. The T waves were upright in Leads 1 and 2 and diphasic in Lead 3. Diagnosis: normal mechanism. Left axis deviation.

The final clinical diagnoses were: (1) congenital heart disease, patency of the interventricular septum, rheumatic heart disease with mitral stenosis and insufficiency; (2) endocarditis — subacute bacterial; (3) embolism — left femoral artery.

Postmortem Examination

The autopsy was performed three hours after death; only the findings bearing on the subject are included.

The body is poorly developed, emaciated and weighs 106 pounds. The mucous membranes, the nail beds and ears are deeply cyanotic. There is marked clubbing of the terminal phalanges of the fingers and toes. The entire left gluteal region and left lower extremity have a gray-purple, mottled appearance. The skin covering this

extremity is tense, shining, and pitting edema is present throughout. Upon opening the abdominal cavity about 60 cc. of clear amber-colored fluid is found. The liver extends well below the costal margin. When the chest plate is removed, it is found that the transverse diameter of the heart is greatly increased, measuring 13 cm., while that of the thorax measures 19 cm. The pericardial surface is smooth and the pericardial sac contains about 30 cc. of a clear amber-colored fluid. The apex of the heart is blunt and the distance from the apex to the base is relatively short, giving the heart as a whole a spheroidal shape (Fig. 1). One large vessel only arises from the base, at the usual site of the origin of the pulmonic and aortic arteries (Fig. 2). The heart and lungs are, therefore, removed *en masse* together with the upper three-fourths of the thoracic aorta.

Heart: The heart is large, firm and estimated to weigh over 600 gm. A normal amount of subepicardial fat is present along the course of the coronary arteries. The right auricular appendage is large and passes well around the front of the common truncus arteriosus. No pulmonary artery or ductus arteriosus are found. The base of the common truncus measures 9 cm. in circumference. At its junction with the transverse portion of the vessel it gives rise to the right innominate, left common carotid and left subclavian arteries, in the usual manner. Beyond this point the circumference of the vessel decreases in size, measuring 6 cm. From here the vessel follows the normal course of the thoracic aorta and, aside from the vessels to be described, gives rise to the arteries usually derived from this vessel. Distal (1.5 cm.) to the origin of the left subclavian artery, the common truncus gives rise to a small artery measuring 5 mm. in diameter (Fig. 1, No. 1). This vessel passes to the right of and posterior to the trachea, entering the upper lobe of the right lung. On the same side, 3 cm. beyond this point, another vessel of the same diameter arises (Fig. 1, No. 2). This also passes to the right, just below and posterior to the bifurcation of the trachea, to enter the middle lobe of the right lung, dividing into two branches as it passes to this lobe. Beyond this vessel 1 cm., another artery is given off from the left side of the common truncus and runs to the hilum of the left lung (Fig. 1, No. 3). Just beyond the point of entrance into the lung it divides into three branches, one passing into the upper, and two into the lower lobe. At the

posterior medial aspect of the lower lobe of the right lung is found still another vessel passing from the organ at this point (Fig. 1, No. 4). This measures about 5 mm. in diameter; it is thin-walled and is probably a vein passing out of the substance of the lung. Its point of termination is destroyed on removal of the organ. The truncus, at the level of the third thoracic vertebra, just below the pulmonary vessels described, measures 4.5 cm. in circumference.

The right auricle is approximately two-thirds as large as the left. The foramen ovale is closed. In general, the wall of the right auricle is thicker than that of the left by 1 mm. The superior and inferior vena cavae, the coronary and pulmonary veins, open into the auricle in the usual manner. The right ventricular wall measures 13 mm. in thickness and the left ventricular at its corresponding level measures 11 mm. The average thickness of the interventricular septum is 14 mm. In the upper portion of the septum is a defect measuring 2.5 by 1.5 by 1 cm. (Fig. 2). The semilunar cusps of the common truncus lie immediately over this opening. The anterior and posterior boundaries of this defect are formed respectively by the anterior and posterior ventricular walls; the lower boundary is formed by the ventricular septum. There appears to be no remains of the pars membranacea. The common truncus arteriosus arises, therefore, directly over the defect and communicates with both ventricles. The cavity of the right ventricle is nearly twice as large as that of the left. The mural endocardium of all four heart cavities is smooth and glistening. The papillary muscles and the columnae carneae stand out prominently from the ventricular walls. On the tricuspid valves are two healed vegetations which project 1 to 2 mm. above the surface of the valve leaflets on their auricular surfaces. The larger mass measures 4 by 5 mm. and lies on the posterior leaflet; the smaller one measures 2 by 3 mm. in diameter and is situated upon the median leaflet. Most of the chordae tendineae of the posterior leaflet arise directly from the interventricular septum in the upper portion. Those of the median leaflet arise from the lower portion of the septum, while the chordae tendineae of the posterior leaflets arise from the papillary muscles of the right ventricular wall, beneath and posterior to the valve defect. The semilunar cusps of the truncus are three in number and large, formed by a right and left posterior and anterior cusp. The sinuses of Valsalva

are prominent and deep. The right coronary artery arises in the left posterior sinus of Valsalva and the left coronary artery in the anterior sinus of Valsalva. Both coronary openings lie unusually high in the sinuses. On the anterior semilunar cusp is a large vegetation measuring 2.5 by 1.5 by 1.5 cm. (Fig. 2). It is of a greenish red color and has a granular fibrinous appearance. Its base is solid and firmly adherent to the ventricular surface of the cusp. The free portion of the mass is soft and friable. It lies for the most part in the right ventricle and almost completely fills the interventricular defect. Three or four small openings are present near the free edge of the posterior cusp. The intimal lining of the common truncus is smooth throughout. The mitral leaflets are delicate and velamentous and the chordae tendineae insert well beyond the free edges.

From the above description it is seen that the venous blood in the right heart is mixed with the arterial blood of the left, the admixture from both ventricles passing directly into the common truncus arteriosus. This common truncus with its mixed arterial and venous blood distributes a small portion to the lung by way of the pulmonary branches described above, and to the systemic circulation in the usual manner. The return flow from the systemic and pulmonary circulations passes into the left and right auricles respectively in the normal manner, and from the auricles through the usual orifices into the communicating ventricles.

Spleen: The spleen is large and firm. It weighs 500 gm. The capsule at the lower pole is roughened by a fibrinous deposit. The underlying splenic tissue has a dark purplish color as contrasted with the deep red normal-appearing surrounding parenchyma. A cross-section through the center of this lesion and the hilum reveals a cone-shaped area of opaque darkly colored tissue with the apex of the cone toward the hilum, and the base, measuring 6 cm. across, beneath the capsule. An inelastic friable clot is found in a branch of the splenic artery supplying this region.

The lower portion of the left common iliac artery with its branches, the left external and internal iliac arteries, are non-compressible on palpation. Cross-section through these vessels shows their lumina to be entirely occluded by a dark reddish brown inelastic mass.

The following anatomical diagnoses were made at the completion of the autopsy.

Primary: Healed tricuspid endocarditis, acute vegetative endocarditis (valve of the common truncus), infarcts of the spleen, embolus in the left common iliac artery.

Subsidiary: Truncus arteriosus communis persistans, ventricular defect, cardiac hypertrophy, Meckel's diverticulum, accessory spleen.

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DESCRIPTION OF PLATES

PLATE 70

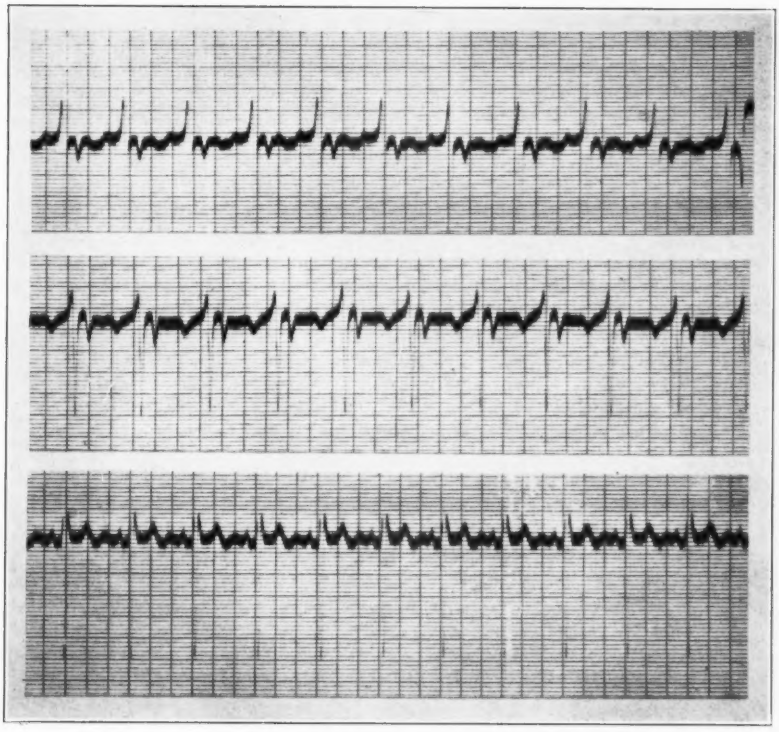
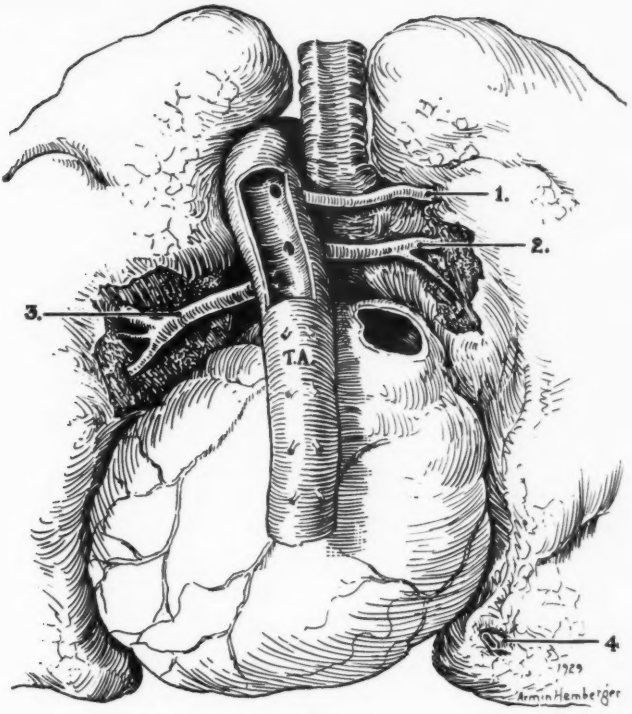


Chart 1

PLATE 71

FIG. 1. A 1862. Posterior view of heart and lungs showing common truncus and origin of pulmonary arteries to lobes of lungs.

FIG. 2. A 1862. Longitudinal section of heart showing common truncus arteriosus and interventricular septal defect.



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MADURA FOOT DUE TO MONOSPORIUM APIOSPERMUM IN A NATIVE AMERICAN*

DOUGLAS M. GAY, M.D., AND JAMES B. BIGELOW, M.D.

(From the Pathological Laboratory of the Boston City Hospital, Boston, Mass., and the Clinic of Dr. James B. Bigelow, Holyoke, Mass.)

Mycetomas are defined by Castellani and Chalmers[1] as "all growths and granulations which produce enlargement, deformity, or destruction in any portion of the tissues of man or animals, and which are caused by the invasion of the affected area by fungi belonging to different genera and species, which produce bodies of varying dimensions, colour, and shape, composed of hyphae, and sometimes chlamydospores, embedded in a matrix. These bodies, which are capable of giving rise to mycelial filaments, on germination, are termed 'grains,' and are found either embedded in the pathological tissue forming these growths and granulations, or escaping freely in the discharge thereform. In addition, eosinophile bodies can usually be seen."

Two kinds of mycetomas are recognized: actinomycosis in which thirteen species of Actinomyces are involved, and maduromycosis in which some fifteen species of various other fungi are the etiological agents. It is remarkable that so great a variety of widely different fungi cause lesions which are clinically almost identical. Mycetoma of the foot is commonly spoken of as Madura foot. The disease is endemic in parts of India and Africa and sporadic in the rest of the world. Boyd and Crutchfield[2] and more recently Gammel[3] reviewed the status of Madura foot in the United States. The latter found twenty-two cases reported, eighteen of these caused by Actinomyces and four caused by other fungi.

One of the rarest fungi causing mycetoma is that generically known as Monosporium, also referred to as Scedosporium. Reports of seven cases of infection with this fungus were found in the literature.

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Review of Literature

Tarozzi [4] isolated and described an organism which he at first mistook for an actinomycete causing a chronic osteomyelitis of the foot. The patient was a male native of Sardinia, 40 years of age, who was suffering from a swollen ankylosed left foot with recurrent pustules and sinuses of four months duration. At the age of 13 years he received a knife wound in the foot. Twenty years later he twisted the foot and was confined to bed a month. From that time on the foot alternately swelled and regressed and the ankle gradually became ankylosed, but no sinuses appeared until four months before operation. The foot was amputated and the patient recovered without incident. The fungus isolated from the tissues of the amputated foot occurred as groups of soft, gray-red granules the size of grains of sand. Although it was cultured and studied, its true nature was not appreciated until two years later when Radaeli [5] isolated and studied an identical fungus from a case of chronic osteomyelitis of the foot, of four years duration in a male Italian. In this case the foot was greatly swollen and deformed in the anterior two-thirds. Recurrent brown to wine-colored swellings and sinuses discharging yellow grains had been present for two years, widely scattered over this area. X-ray showed overproduction of bone in the vicinity of the metatarsals. Despite medical treatment for several months the condition gradually extended to further bone and soft tissue destruction, and painful crises developed which kept the patient in bed for several months at a time. Small, soft, yellow grains transferred from the sinuses to various media gave rise in about three days to small, white, cottony, raised colonies 3 to 5 mm. in diameter. These gradually became brown and extended a short distance into the media. The fungus was further characterized by filiform, interwoven, vegetative hyphae and decumbent, rambling, septate conidiophores 2.5 to 3 microns wide with ascending, somewhat attenuated branches bearing single terminal conidiospores. The conidia were continuous, piriform, oblong, sometimes obovate, truncated at the base, 14 by 5.6 microns, sometimes 11 by 5.7 microns, rarely subround, and red-yellow in color. Saccardo named this organism *Monosporium apiospermum*.

Linhaeres and de Magalhaes [6] isolated a fungus from two cases of mycetoma in Brazil. Although the organism was cultivated with difficulty it is generally considered identical with *M. apiospermum*.

Montpellier and Gouillon [7] report the case of a male Algerian, aged 35 years, who suffered from a chronic osteomyelitis of the left foot following an injury to the plantar surface four years before. The lesion was characterized by the gradual formation of painless swellings which ulcerated and discharged seropurulent material and pale yellow granules. X-ray showed rarefaction of bone with dislocation of the tarsometatarsal joints. The grains were 0.1 to 1 mm. in diameter and sometimes aggregated. A crushed grain showed mycelial segments 2 to 6 microns long, and egg-shaped spores 10 microns in diameter. Cultures were easily obtained on all moist media and, in addition to the usual form of growth, a slower, wrinkled, mottled brown, scantier and less downy type sometimes occurred without obvious reason. Both types of culture grew the same in hanging drop. A three-day-old culture showed radiating septate mycelia 2 to 4 microns in diameter with usually alternate branches at wide angles. The oldest hyphae tended to be moniliform. Granules were irregularly distributed through the protoplasm. Numerous terminal spores were present. On the fifth day the moniliform character was prominent and the protoplasm was condensed into two or three (usually two) masses resembling nuclei in each cell. On the eighth day many of the segments showed subdivision, isolating two oidia, each containing a nucleus. The spores were increased in number with the age of the culture and depended on oxygen for their formation. They were slightly egg-shaped, 6 to 10 microns in diameter, and terminal or lateral in position. These authors consider the organism identical with that reported by Radaeli but believe it to be an Aleurisma and not a Monosporium.

Fonseca and de Arêa Leão [8] studied cultures of this organism which they isolated from a patient with yellow-grain mycetoma. In addition to confirming the cultural findings of others they observed the formation of sclerotia in fluid media and in the very moist portions of solid media. Two other forms of reproduction were also described: crescentic terminal single spores attached to the hypha by one end of the crescent, and abundant terminal or intercalary chlamydospores with thickened walls and frequent characteristic small protuberances.

The only other reference found of infection by a fungus of the genus Monosporium is that of Pepere [9] who studied a case of Madura foot of eighteen years duration in an Italian peasant 33 years of

age. The various tissues in the foot were involved, and black, or red-black, firm grains 1 to 2 mm. in diameter were obtained from the lesion. The grains were composed of densely matted, coarse, yellow-brown filaments and chlamydospores. Although original cultures were obtained with difficulty, subcultures grew readily and the growth remained white. The hyphae were 3 to 4 microns in diameter, septate and gave off a few branches at diverse angles. Older hyphae sometimes measured 5 to 5.5 microns. Fertile hyphae were erect and decumbent, and shorter and wider than vegetative mycelia. Conidiospores were terminal, single, piriform, with truncated base, and measured about 12 by 5 microns. Under unfavorable conditions sclerotia were formed which were considered analogous to the grains formed in the tissues of the host. This is *M. sclerotiale* and differs from *M. apiospermum* in the black color of the grains, slow-growing white colonies, precocious formation of sclerotia, and short, wide fertile branches.

Twenty-six species of Monosporium are listed by Saccardo [10] and two others are listed by Farlow [11]; none of these, however, resembles the pathogenic forms described in this paper. In 1911 Saccardo suggested the generic name Scedosporium to include the pathogenic species apiospermum and sclerotiale but no definite evidence could be found that the genus was officially erected.

The case of Madura foot described below is apparently due to *Monosporium apiospermum.*

Report of Case

A native white American male, aged 33 years, applied in December, 1928, for treatment of recurrent swelling and ulceration of the right foot of about ten years duration. He has always lived in Holyoke, Massachusetts, with the exception of eight months in 1920 and 1921 when he was stationed with an artillery unit of the United States Army in the state of Oklahoma, and he has never been outside of the United States. About ten years ago the patient had a lesion over the second metatarsal bone of the right foot which he thought was an injury received while playing football. This was in the nature of an inflammatory process with the slow formation of pustules which opened to the surface, discharged reddish yellow pus, and then healed promptly. While in Oklahoma the patient frequently went swimming barefooted and at this time identical

lesions appeared near the same site and went through the same process of discharging pus and then healing. Since then about twelve similar lesions have appeared from time to time at various sites on the right foot and ankle, and for some years the patient has noticed small yellow grains in the discharge. A typical lesion begins with a small, localized, non-tender swelling which appears somewhere beneath the skin of the foot. It increases in size for several weeks and the overlying skin becomes involved, turns bluish red and ruptures at the central point. The sinus thus formed discharges thin serous fluid, more or less pus, and numerous firm yellow grains up to 1 mm. in diameter. After a period varying from several days to several weeks, the sinus closes leaving a superficial depressed scar. The process has not extended to the toes or to the fibula and tibia. The foot has increased slightly in size and X-ray plates show an overproduction of bone in relation to the os calcis, cuboid and second metatarsal bones. The foot has not prevented the patient from walking about and working until about a year ago when for periods of several days to two weeks there has been severe pain, especially when bearing weight on the foot. The general health is good. Wassermann and Kahn tests of blood taken March 21, 1929 were negative. Red and white blood cell counts on the same date were within normal limits. Although the patient frequently sought medical aid, no form of treatment, including fairly large amounts of iodides, influenced the progress of the disease, and apparently the correct diagnosis was not made until tissue removed December 20, 1928 was examined microscopically. Amputation has been advised, but is refused by the patient. Fig. 1 shows the appearance of the foot in January, 1929.

Microscopic Examination

The tissue shows small irregular islands of new bone embedded in granulation tissue which is markedly infiltrated with lymphocytes, plasma cells and numerous endothelial leucocytes. Here and there are masses of polymorphonuclear leucocytes, usually with centrally located fungus grains up to 0.5 mm. in diameter (Fig. 2). Each small abscess is surrounded by a zone of endothelial leucocytes, some of which have phagocytosed fragments of other cells. No foreign body giant cells occur in the sections studied. The lesion is a pronounced osteomyelitis which is unusual only because of the

presence of the fungus. The fungus masses are round, lobulated or umbilicated. Stained with hematoxylin and eosin, a section of a typical lobulated grain 0.5 mm. in diameter presents an outer bright red zone 0.02 mm. thick which shades into a colorless zone of the same thickness. In both of these portions of the grain, closely packed round bodies about twice the size of red blood corpuscles, and a few hyphae can be made out. The details of these structures are less distinct toward the middle where the colorless zone merges with an amorphous blue or indifferently staining mass making up most of the granule. The faint outlines of a few hyphae can be made out in the central mass. A section of the same granule stained by the Gram-Weigert method (Fig. 3) shows a narrow outer Gram-positive zone of radiating, occasionally branching, coarse hyphae with numerous intercalary and terminal swellings (chlamydospores), and a central Gram-negative amorphous mass in which there are a few Gram-positive hyphae. Although no isolated organisms occur in the tissue, a few faint-staining hyphae project from the margin of the granule.

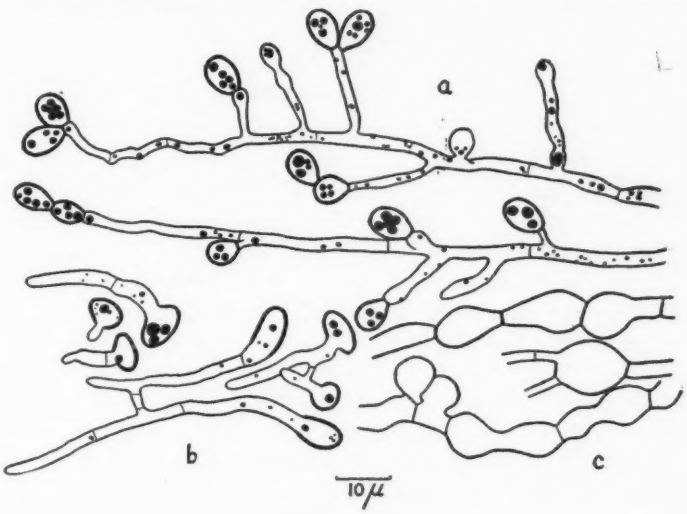
Biological Characteristics and Pathogenicity

Cultures of the fungus were made one month after the biopsy, at which time there were two small sinuses in the dorsum of the foot at the site of the biopsy incisions, and a third sinus on the instep. A small amount of sanguinopurulent discharge was present and about twelve light yellow, firm granules up to 1 mm. in diameter were removed from two sinuses. The granules were washed in plain broth, planted on a variety of media, and incubated at 37° C. and at room temperature. Two months later more grains were obtained from one of the sinuses. These gave the same results on cultivation.

The growth is the same on plain agar, serum agar, Sabouraud's agar, blood agar, and dextrose agar, and in initial cultures occurs only where a grain is deposited. Growth is rapid at 37° C. and slower at room temperature. After two days incubation at 37° C. a round, white, cottony mass of hyphae surrounds the granule. Growth proceeds laterally and in four days the center becomes gray-brown. The growth progresses with a narrow, white, advancing margin and eventually the surface of the medium becomes covered with a black surface layer, a velvety brown aerial layer which extends at most 4 mm. above the surface, and a few colorless hyphae extending to an

equal depth into the medium. The organism does not grow when grains are inoculated beneath the surface of solid media.

Young hyphae in the white margin of growth are filiform, straight or slightly curved, septate, branch frequently at an angle of 30 to 90 degrees, and occasionally anastomose. The diameter averages 2.9 microns. The only other visible structures in the hyphae are a few round refractile bodies up to 2 microns in diameter scattered



TEXT-FIGURE 1

Growth of *Monosporium apiospermum* on Sabouraud's agar at 37.5° C.

(*a*) Conidiospore formation, 5 days incubation.
(*b*) Sprouting conidiospores, 18 hours incubation.
(*c*) Chlamydospores, 18 days incubation.

throughout. Older hyphae from the brown portion of the colony show many erect and decumbent spore-bearing branches (conidiophores) which in turn are branched (Text-Fig. 1 (*a*)). In structure these do not differ essentially from the sterile hyphae. The conidiospores are terminal, usually single, and occasionally in pairs side by side or end to end. Some are borne on short, narrow, straight sterigmata arising perpendicularly from the larger hyphae. The conidiospores are brown, thick-walled, egg-shaped, with the smaller slightly flattened end attached to the conidiophore or sterigma, and measure 9.4 microns long by 4.9 microns in greatest diameter. Each

spore contains several round refractile bodies similar to those in the hyphae. Conidiospores germinate promptly when subcultured. Within twelve hours at 37° C. a hypha sprouts from the side or small end (Text-Fig. 1 (*b*)) and growth proceeds as in original cultures. Germination was never observed in spores previous to separation from the conidiophore. With age the hyphae become more closely segmented, irregular in outline, and frequently form terminal or intercalary swellings up to 10 microns in diameter (Text-Fig. 1 (*c*)). These are interpreted as chlamydospores. Chlamydospore formation is seen only on and beneath the surface of the medium while conidiospores are on the surface, aerial, and occasionally beneath the surface. Among the aerial hyphae of an eighteen-day culture on Sabouraud's medium there are a few round bodies up to 56 microns in diameter interpreted as sclerotia (Figs. 4 and 5). These are shells of densely interwoven hyphae and contain a substance of indefinite structure which stains poorly.

A grain in nutrient broth incubated at 37° C. develops in a week into a small white cotton-ball colony in the bottom of the tube but does not form spores and the supernatant medium remains clear. Subculture to the surface of broth media gives rise to a felted white growth which remains on the surface and eventually turns brown with the formation of conidiospores.

Blood serum and egg medium are liquefied. In the lower, very moist portion of the medium the growth takes the form of a shining, black, wrinkled, tough membrane composed of densely packed hyphae and conidiospores of twice the usual length.

Gelatin is not liquefied. Dextrose and lactose are fermented with the formation of gas. Neither acid nor gas is formed from saccharose.

Two white mice were inoculated intraperitoneally with grains obtained directly from the lesions, and two other white mice received intraperitoneal injections of a three-weeks-old broth culture containing many spores. The animals were observed for one month and no ill effects were noted. No lesions or fungus were found at autopsy. A guinea pig injected with a young broth culture containing hyphae and spores remained well during one month of observation. An old culture containing many spores and hyphae was injected into the foot of another guinea pig without result.

TABLE I

		M. apiospermum	Authors' fungus	M. sclerotiale
Grains	color	yellow	yellow	
	size	0.1 to 3 mm.	up to 1 mm.	1 to 2 mm.
Growth		2 to 12 days	2 days	4 to 5 days
Colony	color	white to brown to black	white to brown to black	remains white
	size	small	large	large
Hyphae	in tissue	1 to 1.5 μ	1.3 μ	1.2 to 1.5 μ
	in culture	2 to 4 μ	2.9 μ	3.4 μ
Chlamydospores	in tissue	10	about 14	present
Fertile hyphae		decumbent and erect	decumbent and erect	decumbent and erect
	size	2.5 to 3 μ	2.9 μ and less	shorter and thicker than mycelium
Conidia	shape	ovoid, truncated	ovoid, truncated	ovoid, truncated
	size	4 to 6 by 10 to 14 μ	4.9 by 9.4 to 18 μ	
Sclerotia		occasional	occasional	numerous

The only other organism encountered in original cultures was a small Gram-negative bacillus corresponding in appearance to an organism seen in smears from the lesions. It was looked upon as a sapropyhtic invader without significance.

While the characteristics of *M. apiospermum* have been established piecemeal by the various observers and have varied somewhat, the identity of the fungus which we isolated is shown in Table I.

Discussion

Although Madura foot is a rare disease in the United States, it should be considered in chronic osteomyelitis of the foot. It is usually easy to find the grains and their presence is pathognomonic, but the identification of the infecting organism requires microscopic and cultural study. Diagnosis by biopsy is impossible unless a grain is included in the section, because the lesion is not histologically characteristic. It may be a simple chronic osteomyelitis, resemble tuberculosis, or occasionally simulate lues. The patient with Madura foot, especially of the yellow-grain variety, should be started on iodine therapy, unless there is some contra-indication for the drug, because of the well known response of Actinomyces and Sporotrichum infections to iodine. Should the organism prove to be some other type, amputation is the only treatment which promises success.

Summary

1. A case of Madura foot due to *Monosporium apiospermum* is reported.

2. The literature on pathogenic Monosporia is reviewed.

Note: We are grateful to Dr. C. W. Dodge for assistance with the mycology.

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DESCRIPTION OF PLATES

PLATE 72

FIG. 1. Madura foot of 10 years duration due to *Monosporium apiospermum*. Two healing biopsy wounds are situated on the dorsum and below the malleolus. Several spontaneous lesions in various stages of swelling, sinus formation and healing are also evident.

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Gay and Bigelow Madura Foot Due to Monosporium Apiospermum

PLATE 73

FIG. 2. Microscopic appearance of the lesion of Madura foot due to *Monosporium apiospermum*. There is a chronic osteomyelitis with an abscess containing a grain of the fungus. × 40.

FIG. 3. Section of a grain stained by the Gram-Weigert method. The grain is umbilicated and composed of a central homogeneous mass of dead fungus surrounded by a marginal network of branching hyphae and chlamydospores. × 250.

FIG. 4. Section of an eighteen-day culture of *M. apiospermum* on Sabouraud's medium. A growth of hyphae and conidiospores extends into the medium (lower portion of photograph) and for some distance above the surface where conidiospores are most numerous. Four sclerotia are shown. × 200.

FIG. 5. Sclerotia. These are composed of dense shells of hyphae. × 750.

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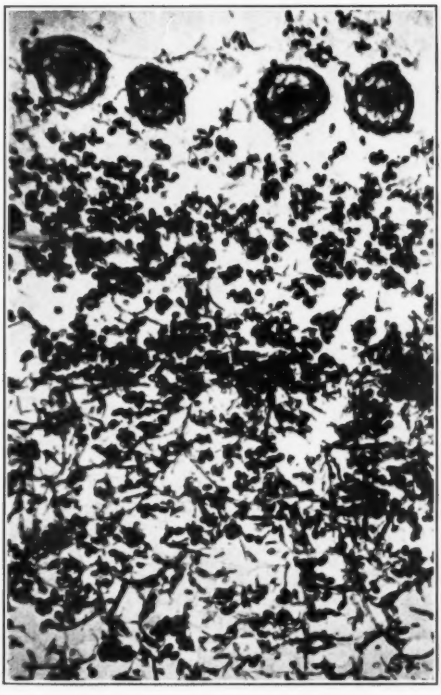

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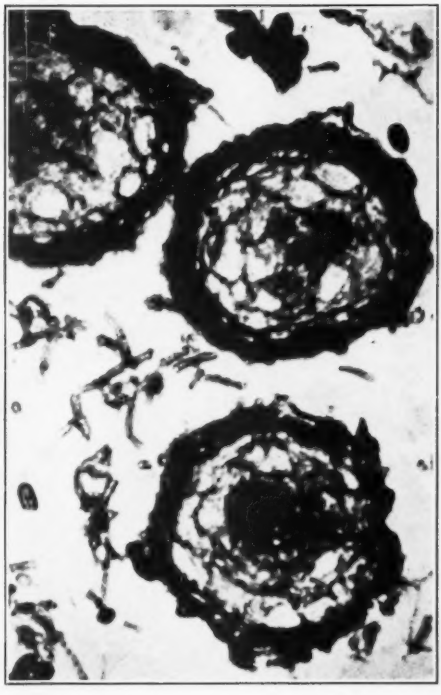

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Gay and Bigelow

Madura Foot Due to Monosporium Apiospermum

THE CALCIFICATION OF TUBERCLES BY MEANS OF IRRADIATED ERGOSTEROL *

TOM DOUGLAS SPIES

(From the Pathological Laboratory of the Boston City Hospital, Boston, Mass.)

Since the observations of Steenbock [1] and Hess [2] that certain substances acquire antirachitic properties following exposure to ultraviolet light, there has been a great deal of interest centered on the artificial production of vitamin D and on its application to the diseases concerned with calcium metabolism. The production of a potent antirachitic substance by the activation of cholesterol initiated careful chemical studies of this substance. In 1926 Rosenheim and Webster [3] demonstrated that ergosterol acquires remarkable antirachitic power following activation, and that cholesterol loses activatability on purification. Heilbron, Kamm and Morton,[4] Pohl,[5] and Windaus and Hess [6] could identify by spectroscopic study three absorption bands found in cholesterol as characteristic of the vitamin precursor. Bills and his co-workers [7] discovered a fourth absorption band identified with the provitamin, and were further able to show by a comparison of destruction rates that the activatable contaminant of cholesterol was ergosterol. As a result of all these observations it became generally accepted that the specific substance activated by irradiation was ergosterol, a sterol widely distributed in nature.

The efficacy of this substance in the treatment of rickets and osteomalacia has been established. In addition, a few workers (Pfannenstiel,[8] Kreitmair and Moll,[9] Klein,[10] and Smith and Elvove [11]) have studied the effects of massive doses of this material on normal animals. They have found an elevation of the blood calcium followed by calcium deposition in some of the tissues. In a similar study (to be published later) we have found that there is usually a retention of nitrogenous products in the blood before death. The animals showed extensive calcium deposits in the arterial walls, lungs, kidneys, stomach wall, heart muscle, bronchial

* This study has been aided by a contribution from Mr. William A. Parker.
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cartilages, spleen, ovaries and adrenals. It is worthy of note that calcium deposits were not present in the liver or striated muscle.

In view of the specific manner in which irradiated ergosterol induces calcium deposition in certain tissues while sparing others, it seemed of interest to study its action in certain pathological conditions. The administration of this substance to animals having tuberculosis at once suggested itself, since the caseous portions of tubercles appeared to be especially favorable material for calcification. Rabbits were used because of their great susceptibility to irradiated ergosterol. In order to eliminate the spontaneous calcification that sometimes occurs in chronic tuberculosis of rabbits, a highly virulent strain of bovine tuberculosis was chosen.

Reports of the calcification of the lesions in acute tuberculosis in animals following the administration of irradiated ergosterol have not been found in the literature.

Material and Methods

Each of twenty-five young rabbits, averaging 1700 gm. in weight, was given intravenously 1 cc. of a heavy saline suspension of highly virulent bacilli of bovine tuberculosis. Later, a concentrated preparation of activated ergosterol, having one thousand times the antirachitic potency of cod liver oil,* was administered by stomach tube to each of fourteen of the above rabbits in individual doses of 3 to 5 cc. (Table I). This medication began on the thirteenth day of the experiment with the exception of three rabbits, Nos. 13, 14 and 18, which were started on the seventh, tenth, and tenth day of the experiment, respectively. The administration was continued at frequent intervals (one to three days) until death occurred. The interval between doses and the amount of material per dose was decided individually for each animal after careful consideration of its condition. At all times, the decision was made with a view of prolonging the period of medication rather than of giving large individual doses.

A series of six of the remaining animals were given comparable doses of the inert solvent oil used in the above preparation.

The remaining five rabbits received no medication and served as additional controls.

* This preparation was furnished through the courtesy of Mead Johnson & Co.

All animals were allowed to die. Sections from the organs were fixed in an alcohol-formalin mixture (9 parts of 95 per cent alcohol to 1 part of 40 per cent formalin), in 10 per cent formalin, in 95 per cent alcohol, and in Zenker's fluid. Some of the tissues fixed in formalin were embedded in celloidin and later stained either with hematoxylin and eosin or by the silver method of von Kossa. In order to study the relationship of the tubercle bacilli to the calcified deposits it was found necessary in staining the tubercle bacilli to avoid the use of acid alcohol which dissolved out the calcium. Therefore, sections stained with carbol fuchsin were cleared in aniline oil following the method of Flexner for staining the bacillus of leprosy. In order to demonstrate fat, frozen sections of formalin-fixed material were stained with Sudan IV. The tissues fixed in Zenker's fluid were embedded in paraffin and stained with eosin-methylene blue, and by the usual method for the demonstration of tubercle bacilli in sections. The calcium deposits were identified by their solubility in acid and by the following histological criteria, using formalin-fixed material: (1) when stained with hematoxylin and eosin the precipitated calcium appeared as a dark blue, coarsely granular material; (2) after treatment with a silver nitrate solution and counterstaining with 0.5 per cent basic fuchsin the deposits assumed a deep brownish black color.

Observations

After a period of approximately ten days, all the animals began to lose weight rapidly and died before the twenty-fourth day of the experiment. Diarrhea played a part in causing the death of rabbits No. 7, 8, 9, 11 and 13, soon after receiving their initial dose of irradiated ergosterol.

While all the organs were examined grossly and microscopically in every animal, only the changes in the lungs, kidneys and aorta are regarded as sufficiently significant to warrant their description in this report. Since macroscopically the lungs and kidneys of the animals which received irradiated ergosterol appeared identical with those of the controls, it is thought that one description will suffice for both. On the other hand, the aortae of the two groups will be described separately as some of the aortae from the animals which were given irradiated ergosterol showed definite macroscopic changes which were not present in those of the control animals.

Pathological Description

Lungs: The pleural surfaces were roughened by innumerable small, rounded, grayish yellow nodules (tubercles) averaging 0.2 cm. in diameter. The cut surface of the parenchyma was studded with closely approximated, rounded lesions (tubercles) of similar size. Occasionally a creamy white exudate filled the larger bronchi. The pulmonary vessels were negative.

Kidneys: The kidneys were of normal size and shape. Over the surface were irregularly scattered small grayish white nodules (tubercles). Similar lesions were found within the parenchyma. Pelves, ureters and vessels were negative.

Aorta: Two of the fourteen animals which received irradiated ergosterol (Nos. 14 and 18) showed considerable changes in the upper portion of the aorta. Both had a moderate degree of dilatation of the ascending aorta and the arch. A sclerotic process characterized by the formation of irregular depressed lesions of the wall was very evident from the external surface. The intimal surface was roughened by depressions irregular in size and shape, ranging from 0.4 cm. to 0.1 cm. in diameter. The largest lesions were found in the upper portion of the thoracic aorta where only minute partitions separated their adjacent edges. The number and size of these lesions progressively decreased as the bifurcation of the iliacs was approached. The lining of the depressions was firm, and no evidence of ulceration was seen. The elasticity appeared fairly normal. A faint grayish white line (calcium) was seen in the media. Three of the remaining animals showed very slight roughening of the intimal surfaces of the aorta. The remaining nine animals showed no demonstrable gross lesions of the aortae.

The aortae of the eleven control animals were normal.

Microscopic Description. Formalin Fixation

Lungs: Many large and small areas of calcification were contained in the caseous and necrotic centers of otherwise typical tubercles (Figs. 1 and 2). The deposits were irregular in shape and ranged in size from 0.2 cm. to 0.01 cm. In contrast, the tubercles without necrotic centers rarely contained even a minute trace of deposited calcium. Enmeshed within the calcified centers of the degenerated tubercles were many necrotic cells, acid-fast bacilli and

fat globules. The central portions of the tubercles were surrounded by a well demarcated margin of connective tissue cells, lymphocytes and endothelial and polymorphonuclear leucocytes. This zone was free from calcific deposits. In no instance was there an apparent change in size, shape or cellular content of the tubercles following the deposition of calcium. In contrast to the majority of the animals, Nos. 14 and 18 exhibited a marked preponderance of non-caseating tubercles over the caseating type and, as in all the other cases, calcium deposition was limited almost entirely to the degenerated lesions. These two animals also showed considerable calcification of the bronchial cartilages, bronchial epithelium and alveolar epithelium. The alveoli were often filled with a serous exudate containing endothelial and polymorphonuclear leucocytes. Occasionally some of the bronchi were filled with an acute inflammatory exudate. Calcification was absent within the vessel walls.

Calcium deposits were absent within the lungs of the five animals which received only one dose of activated ergosterol as well as in the eleven control animals, despite the fact that all contained many caseous and necrotic tubercles.

Kidneys: Seven of the animals which received activated ergosterol exhibited calcification in the kidneys. The deposits were prominent in rabbits No. 14 and 18 where both the tubercles and the renal arteries and tubules were conspicuously involved. The kidneys of rabbits No. 2, 20, 22, 23 and 24 contained very scant deposits of calcium which were limited almost entirely to the tubercles and to the walls of the vessels enclosed by them. In general the tubercles in the kidneys were smaller, contained fewer areas of necrosis, and fewer and smaller deposits of calcium than the tuberculous lesions of the lungs. Since the tubercles were of hematogenous origin they were almost always situated around the arteries. The areas containing necrotic cells, polymorphonuclear and endothelial leucocytes were situated nearest to the arterial walls, and exhibited a greater tendency to undergo calcification than the non-necrotic portions of the tubercles. The amount of precipitated calcium was especially prominent in the renal tubules of rabbits No. 14 and 18. It was located in and near the membrana propria, and within casts in the lumina of the tubules. These animals showed large deposits of calcium in the media of the middle-sized and smaller arteries.

The kidneys of the eleven control animals contained similar tubercles but did not contain precipitated calcium.

Aorta: The aortae of five of the animals which received activated ergosterol contained calcium deposits within the media. In every instance they were limited to the internal elastic lamina and adjacent portion of the media. In rabbits No. 14 and 18 the process was extensive and formed an irregularly thickened calcific ring which involved almost the entire width of the media. In rabbits No. 1, 22 and 23 the deposits of calcium were less extensive and had not fused to encircle the lumen. The calcified areas were irregular in size and shape, and their adjacent edges were separated by normal tissue. The remaining nine animals did not exhibit calcification of the aorta.

The aortae from the eleven control animals were normal.

Zenker's Fixation

Calcification was absent in all tissues fixed in Zenker's fluid because the acetic acid had removed the precipitated calcium from the tissues.

Lungs: The tubercles of the lungs appeared identical in the animals which received irradiated ergosterol and in the control animals.

Kidneys: The tubercles were identical in all animals. Occasionally a faint bluish zone, where calcium had been removed, could be seen in the arteries of some of the rabbits showing the most marked calcification in the formalin-fixed preparations. The cells in this region appeared essentially normal.

Aorta: An irregular dark blue-staining rim of tissue in which nuclei and cell boundaries were easily recognized occupied the location of the calcium deposits in the region of the internal elastic lamina. The remaining portions of the wall were quite normal. A slight but similar change was present in the animals showing less calcification. The remainder of the aortae in this series were negative.

The aortae of the controls were negative.

Discussion

It has been shown in the experiments reported here that marked calcification of the caseous and necrotic centers of the tubercles of the lung can be produced by the administration of large doses of

TABLE I

The Effect of Large Doses of Irradiated Ergosterol upon Rabbits with Acute Tuberculosis

Experiment Number	Duration of medication	Total dose	Number of doses	Died: day of exp.	Initial weight	Calcification of lung	Calcification of kidney	Calcification of aorta
	days	*cc.*			*gm.*			
1	10	15	3	23rd	1410	Marked	0	Slight
2	10	15	3	23rd	1370	Marked	Slight calcification in vessels within tubercles	Slight
7	4	5	1	17th	1800	0	0	0
8	1	5	1	15th	1900	0	0	0
9	3	5	1	17th	1920	0	0	0
11	3	5	1	17th	2020	0	0	0
13	3	5	1	10th	1950	0	0	0
14	8	20	4	15th	2060	Calcification of caseous centers and of alveolar and bronchial epithelium	Considerable	Considerable
18	8	15	3	18th	2100	Calcification of caseous centers and of alveolar and bronchial epithelium	Considerable	Considerable
20	7	15	4	20th	1700	Marked	Slight calcification only in tubercles	0
21	4	6	2	16th	1740	Marked	0	0
22	8	14	4	21st	1900	Marked	Very slight	Slight
23	8	14	4	20th	1650	Marked	Slight in tubercles	0
24	7	11	3	19th	1720	Marked	Slight in tubercles	0

activated ergosterol in the last stages of acute tuberculosis in rabbits. That there is a definite tendency for the calcium to precipitate where there is necrosis is shown by the fact that non-necrotic tubercles of the same age do not contain calcium deposits. There is also a tendency for the calcium to precipitate in non-tuberculous locations (kidneys and aorta). However, it has been demonstrated that in some instances large areas of calcification are found in the tubercles with little or no calcification in the normal tissues. It is noteworthy that the five rabbits which received only one dose of irradiated ergosterol did not show any calcium within the tissues.

The dangers of applying these facts to clinical practice are obvious when the toxic manifestations of large doses of irradiated ergosterol are observed in normal animals. We have corroborated the findings of other workers, showing that there occurs a marked loss of weight, cachexia, and calcification of many of the tissues. In addition, we have been able to demonstrate even more widespread calcification than had previously been observed and a retention of nitrogenous products in the blood, associated with marked kidney lesions.

Whether or not these calcium salts would be reabsorbed if the animals lived we are unable to say. It seems likely that other acute inflammatory lesions might also undergo calcification following the use of large doses of irradiated ergosterol.

It should be emphasized that the calcified lesions described in this paper were produced by the use of repeated massive doses of irradiated ergosterol. Single large doses have no such effect.

Summary

1. The administration of repeated large doses of activated ergosterol to rabbits suffering from acute tuberculosis causes extensive deposition of calcium salts within the caseous lesions. The administration of a single large dose produces no demonstrable changes.

2. It is suggested that a high vitamin D diet might possibly be useful in some cases of pulmonary tuberculosis.

Note: I am indebted to Dr. F. B. Mallory for helpful criticism and for the photomicrographs. I also wish to thank Dr. Frederic Parker, Jr., for his suggestions and criticism.

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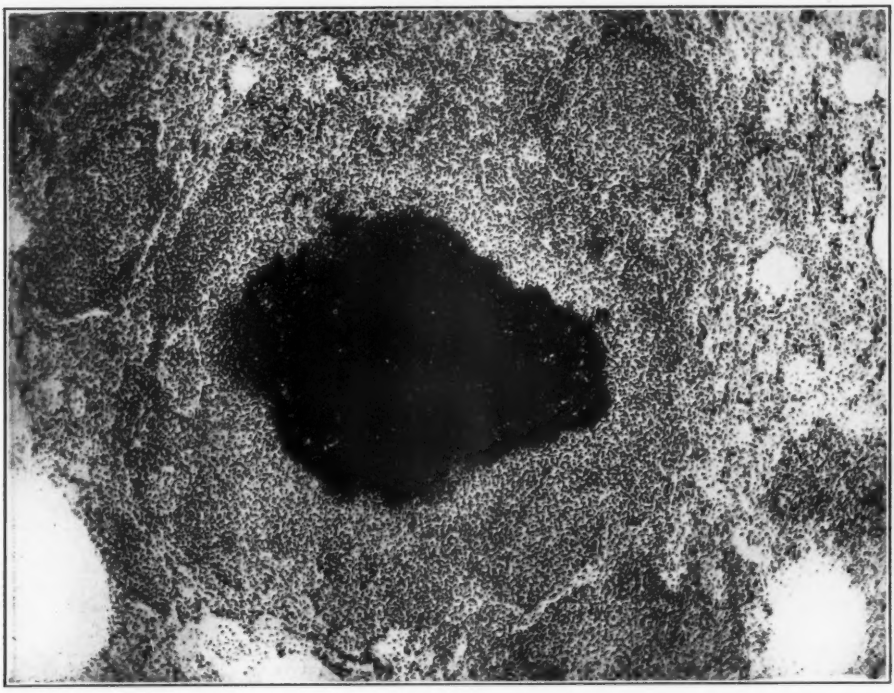
DESCRIPTION OF PLATES

PLATE 74

FIG. 1. Section from the lung. Photomicrograph shows calcification of a caseous center of a tubercle. × 100.

FIG. 2. Section from the lung. Photomicrograph shows calcium deposition within the caseous portions of closely grouped tubercles. × 100.



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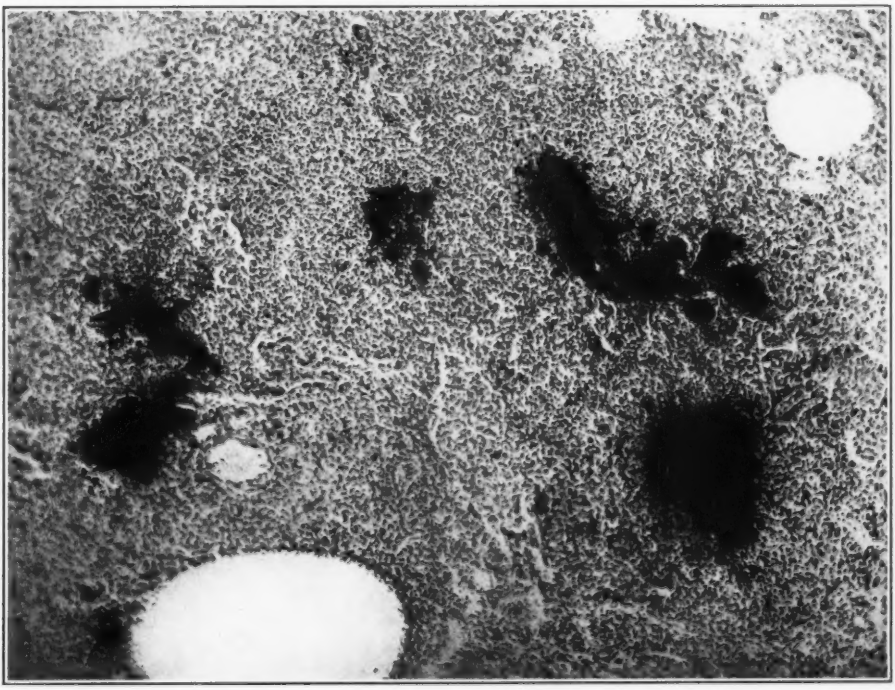

2

Spies Calcification of Tubercles

HISTOLOGICAL CHANGES IN THE RENAL GLOMERULUS IN ESSENTIAL (PRIMARY) HYPERTENSION *

A Study of Fifty-One Cases

Leone McGregor, M.D.
FELLOW OF THE NATIONAL RESEARCH COUNCIL
(*From the Pathological Laboratory of the Boston City Hospital, Boston, Mass.*)

Throughout this paper the term essential (primary) hypertension is used to include all chronic hypertension of unknown etiology. Although this is probably not a homogeneous group, most of the cases are similar clinically and pathologically. They are all characterized by (1) a persistent systolic blood pressure of 150 mm. or more, and (2) a definite left ventricular hypertrophy not associated with any of the diseases known to cause hypertrophy.

The object of this paper is to describe the histological picture of the renal glomerulus in essential hypertension.

The material consists of all the 1927 and 1928 Boston City Hospital autopsy cases which have a history of chronic high blood pressure. After excluding the cases of secondary hypertension due to glomerulonephritis, toxemia of pregnancy, urinary obstruction, nephrosis and aortic insufficiency, there remain fifty-one cases of primary hypertension. The series is subdivided according to the cause of death into (1) a cerebral group (apoplexy) of 16 cases, (2) a cardiac group (myocardial insufficiency and coronary disease) of 19 cases, (3) a renal group (uremia) of 14 cases, and (4) a miscellaneous group (rupture of aorta and diabetes) of 2 cases. The controls are kidneys from nine persons who died in the fifth, sixth, seventh and eighth decades and who were known to have had a normal blood pressure. The object was to determine the glomerular lesions due to age alone.

Before proceeding to a study of these cases, the general conception of the histological changes in the kidney in primary hypertension must be summarized. The work of Johnson,[1] Gull and Sutton,[2] Ziegler,[3] Jores,[4] Herxheimer,[5] Gaskell,[6] Volhard and Fahr,[7, 8, 9, 10, 11] Lohlein,[12, 13, 14] Evans,[15] Fishberg,[16, 17] Jaffe,[18] Bell and

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Clawson,[19] and Klemperer and Otani [20] has shown that the most conspicuous renal lesions are an arteriolosclerosis (a formation of hyalin under the endothelium of the afferent glomerular arterioles) and a hyperplastic elastic tissue intimal thickening of the walls of the small and medium-sized arteries.

In addition Löhlein described a dilatation of the afferent arteriole at its entrance to the glomerular tuft. This finding was confirmed by Fishberg and by Jaffé. Löhlein also observed hyaline areas in the glomeruli continuous with the hyalin of the arterioles. Jaffé suggested that the primary renal lesion be sought in the glomerular tuft where he noted a thickening and hyaline degeneration of the capillary walls.

Volhard and Fahr saw inflammatory glomerular changes in cases of essential hypertension with death from uremia. They believed that the inflammation superimposed on the arteriosclerosis caused the renal insufficiency. Löhlein, Jores and Herxheimer opposed this theory because they thought the glomerular damage was vascular in origin and not inflammatory. More recently Fahr described an acute arteritis of the afferent glomerular vessels as the cause of uremia. Volhard has lately explained the renal insufficiency on the basis of a general vasoconstriction which includes the glomeruli. Fishberg believed the glomerular lesions were non-inflammatory and that uremia was usually due to an acceleration of the arteriosclerotic process. Bell and Clawson found that patients with slowly developing uremia had at autopsy a simple glomerular and tubular atrophy from progressive narrowing of small arteries and arterioles, while those with rapidly developing uremia had a necrosis of arteries and arterioles producing small infarcts, infarcted glomeruli and rarely glomerulitis. Klemperer and Otani ascribed the glomerular changes to ischemia rather than to inflammation.

Technique: The tissues available had all been fixed in Zenker's fluid. The stain which proved most valuable was the Mallory-Heidenhain azan carmine.[21] Unless otherwise stated descriptions of glomeruli are made from this stain. Nuclei are red and all connective tissues including glomerular, capsular and tubular basement membranes are blue. Phosphotungstic acid hematoxylin, Weigert and Verhoeff's elastic tissue stains were used on some of the tissues.

Method of Studying Glomeruli: For practical purposes there are only three types of glomeruli seen in the primary hypertensive

kidney: (1) non-hypertensive glomeruli, some of which may show diffuse or focal inflammatory lesions, (2) hypertensive contracted glomeruli, a few of which may also contain diffuse or focal inflammatory areas, and (3) hyaline glomeruli.

One hundred consecutive glomeruli were counted in each section and classified as (1), (2) or (3). Subheadings under non-hypertensive and under contracted hypertensive were used to indicate the number of such glomeruli showing focal or diffuse inflammatory reactions.

Non-Hypertensive Glomeruli: This term is used to include (1) all normal glomeruli, and (2) all glomeruli which are normal except for focal or diffuse inflammatory lesions.

The reader is referred to a previous paper by the author [21] for a description of the histology of the normal glomerulus. Briefly, the glomerular epithelium and basement membrane are continuous with the tubular epithelium and basement membranes respectively. Likewise, the endothelium of the glomerulus is a continuation of the endothelium of the afferent and efferent vessels. The wall of the tuft contains three structures, which from within out are endothelium, basement membrane and epithelium. These are easily distinguished from one another with the Mallory-Heidenhain azan carmine stain (Figs. 1 and 3).

As Table VI shows, the average percentage of non-hypertensive glomeruli is 20 in the renal group, 44 in the miscellaneous group, 52 in the cardiac group, 63 in the cerebral group and 96.2 in the control group. In the hypertensive series many of these normal glomeruli are hypertrophied in an attempt to compensate for atrophied units.

The inflammatory lesions which occur may be diffuse and involve the whole tuft, or focal and involve only one or two loops. When the whole glomerulus is affected the lesion seems to be identical with that described by the author [22] for acute and chronic glomerulonephritis. However, only a very small number of glomeruli are involved. In early stages the glomerulus is enlarged, the capsular and glomerular epithelium proliferates and the capillary loops are occluded by inflammatory mononuclear cells, swollen endothelium and hyaline fibers (Fig. 5). The latter gradually contract and slowly obliterate the capillary lumen. The end result is a hyaline glomerulus.

Usually only a portion of a tuft is involved. The glomerular

epithelium around the loop, as well as the adjacent capsular epithelium, swells, proliferates and often undergoes hyaline granular degeneration. The lumen of the loop is occluded by fatty swollen endothelium, inflammatory cells, fibrin and hyaline fibers. These fibers, which become collagen, contract and destroy the function of the loop. The adjacent capsular epithelium may proliferate and form crescents. The lobule with the focal lesion often becomes adherent to the capsule during the inflammatory and healing processes.

Glomeruli with focal inflammation are more numerous than those with diffuse involvement. The cerebral group of hypertensives shows the fewest inflammatory lesions while the renal group shows the highest. Every uremic death in this series is associated with inflammatory glomeruli.

The Hypertensive Contracted Glomerulus: (Figs. 2 and 4.) This glomerulus is always smaller than normal, its diameter often being reduced one-half. The decrease in size of the glomerulus produces an apparent increase in the pericapsular connective tissue and gives it a lamellated appearance. The capsular basement membrane is thickened. Its epithelial lining is normal.

The normal glomerular tuft has multiple loops opening out of the main lobules. In a hypertensive glomerulus the original lobulation remains but the loops are decreased in number. This gives the glomerulus a simpler structure. Glomerular epithelium and endothelium are unchanged. The striking feature is a uniform thickening and wrinkling of the glomerular basement membrane. The process seems to proceed diffusely throughout the tuft. Normally the basement membrane is thin and not wrinkled. All transitions from normal are present in one section. In this study only glomeruli in advanced stages of the lesion are counted as hypertensive.

There is no intracapillary impediment to the circulation in such a glomerulus. The afferent arteriole, the capillaries of the tuft and the efferent vessel are always open. The afferent arteriole is not dilated or narrowed at its entrance to the glomerulus.

Occasionally a few of these glomeruli show focal and diffuse inflammatory lesions. The result is occlusion of the whole tuft or part of it and eventual hyalinization. The afferent arteriole usually shows lesions at the hilum of an inflammatory glomerulus.

The percentage of hypertensive contracted glomeruli is 47 in the renal and miscellaneous groups, 33 in the cardiac group, 24 in the cerebral group and 0.8 in the control group (Table VI).

The Hyaline Glomerulus: This type of glomerulus is usually the result of atrophy due to sclerosis of arteries or arterioles. Herxheimer has shown that a small percentage is congenital. The others are due to the healing of inflammatory processes. The latter explanation applies particularly to hyalinization of single loops or lobules.

Glomeruli which atrophy following disease of arteries are usually found in wedge-shaped cortical areas. Those which atrophy due to arteriolar disease are often scattered in groups throughout the kidney. All transition stages between hypertensive and hyaline glomeruli are found in one section. Anilin blue stains the thickened glomerular basement membrane in the midst of the hyaline mass.

The average percentage of hyaline glomeruli is 33 in the renal group, 8 in the miscellaneous group, 15 in the cardiac group, 13 in the cerebral group and 4 in the control group.

Renal Vessels: In this paper the term arteriole is used to indicate the afferent and efferent glomerular vessels, the former arising from the interlobular artery. Serial sections show that the efferent arteriole is normal. The condition of the afferent vessel varies along its course. A distal segment two to three hundred microns long, adjacent to the glomerulus is usually normal. The proximal portion of the arteriole may show an irregular subendothelial fatty hyaline deposit which narrows the lumen. Elastic tissue stains prove that such homogeneous material is internal to the elastic membrane. This type of arteriole may supply (1) an apparently normal glomerulus, or (2) an early hypertensive glomerulus, or (3) a typical hypertensive contracted glomerulus. The arteriolar lesion must then precede or be independent of the glomerular lesion. However, the serial sections show that every hypertensive glomerulus has an afferent vessel which is definitely narrowed and sclerosed in some portion of its course, usually at some distance from the hilum of the tuft. The arteriolar change must, therefore, be related to the basement membrane thickening and wrinkling. The lesions are similar in that the hyaline thickening is subendothelial in both arteriole and glomerulus. Apparently the arteriolar change takes place first.

A dilatation of the afferent arteriole at the entrance to the glomerulus in early cases of hypertension was described by Jaffé and Löhlein. According to my study all normal glomeruli in the control series show this dilatation and only the normal glomeruli in the hypertensive series.

TABLE I

Essential Hypertension (Cerebral Group)

Case number	Age	Sex	Cause of death	Blood pressure	Known duration of symptoms	Summary of history	Blood urea nitrogen	Blood non-protein nitrogen	Urine phenol sulphonephthalein	Heart weight
	years			*mm. mercury*			*mg. per cent*	*mg. per cent*	*per cent*	*gm.*
1	32	f	cerebral hemorrhage	235/125	9 years	9 years ago edema throughout first pregnancy. 5 years ago edema and high blood pressure with second pregnancy. From then on, edema, headaches, dyspnea and nausea. Fundi show exudate and old scars.	..	28	30	370
2	42	m	"	190/120	?	Sudden loss of consciousness.	..	..	..	350
3	43	f	"	270/130	6 months	Not well for past 6 months. 5 days ago became delirious then stuporous.	..	48	..	410
4	48	m	"	200/120	15 years	Cerebral shocks 15 years ago, 5 years ago and 4 days ago. Headaches and high blood pressure for years.	..	..	..	500
5	49	f	"	185/115	?	Sudden loss of consciousness.	..	..	..	400
6	53	f	"	230/130	?	Sudden loss of consciousness.	..	..	..	500
7	55	m	"	230/140	2½ years	Sudden loss of consciousness.	..	..	..	540
8	60	m	"	250/110	several years	High blood pressure for several years. 4 days ago a cerebral accident.	..	..	..	370
9	60	f	"	155/110	20 years	20 years of palpitation and dyspnea on exertion. 5 years of attacks of angina, failing vision and nocturia. 4 days of cyanosis, peripheral edema and coma.	..	..	..	530
10	65	m	"	150/95	?	Admitted comatose, cyanosed with edema of legs one day after cerebral accident.	..	..	..	550
11	68	f	"	245/120	3 years	3 years of treatment for high blood pressure. 2 weeks of weakness, dizziness and headaches. Vessels of fundi tortuous. One day ago a sudden cerebral accident.	..	..	..	420
12	70	f	"	high	3 years	3 years ago had high blood pressure and a cerebral shock. Admitted in coma.	..	..	..	350
13	71	m	"	220/140	10 years	10 years of periodic dyspnea and edema. 2 years ago high blood pressure and a cerebral accident. Admitted in coma.	..	37	..	500

TABLE I

Essential Hypertension (Cerebral Group)

Coronary sclerosis	Mural thrombosis	Weight of kidneys	Sclerosis small and medium-sized renal arteries	Sclerosis of renal afferent arterioles	Tubular atrophy	Glomeruli						
						Non-Hypertensive			Hypertensive contracted			Hyaline
						No inflam.	Focal inflam.	Diffuse inflam.	No inflam.	Focal inflam.	Diffuse inflam.	
		gm.				*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
–	absent	210	+++	++++	++	44	..	..	30	..	..	26
–	absent	158	++	++	+	55	..	..	34	2	..	9
–	absent	310	++	++++	++	62	..	..	30	..	..	8
++++	present	240	+	+	–	80	..	..	15	..	..	5
+	absent	300	+	+	–	70	..	..	22	..	..	8
++	absent	200	+	++	+	77	..	..	21	..	..	2
–	absent	280	++++	+++	++++	27	..	..	29	..	1	43
–	absent	210	+++	+++	++	48	..	..	40	..	..	12
++++	present	270	+	+	++	34	..	..	30	2	..	34
–	absent	250	+	++	++	57	2	3	20	..	..	18
+++	absent	320	++	+++	++	62	11	..	22	..	..	5
++++	absent	200	++	+	–	75	..	..	20	..	..	5
++++	absent	240	++	+	++	77	..	..	13	..	..	10

TABLE I (*continued*)

Case number	Age	Sex	Cause of death	Blood pressure	Known duration of symptoms	Summary of history	Blood urea nitrogen	Blood non-protein nitrogen	Urine phenol sulphonephthalein	Heart weight
	years			*mm. mercury*			*mg. per cent*	*mg. per cent*	*per cent*	*gm.*
14	72	m	cerebral hemorrhage	180/90	15 years	15 years ago a cerebral accident. Two more while in hospital with erysipelas.	..	42.5	..	350
15	77	m	"	220/115	?	19 days ago a cerebral accident. Coma and hemiplegia since then.	..	..	..	390
16	80	f	"	210/100	1 year	1 year of high blood pressure, dizziness, nocturia and dyspnea.	..	..	..	320

TABLE II

Essential Hypertension (Cardiac Group)

Case number	Age	Sex	Cause of death	Blood pressure	Known duration of symptoms	Summary of history	Blood urea nitrogen	Blood non-protein nitrogen	Urine phenol sulphonephthalein	Heart weight
	years			*mm. mercury*			*mg. per cent*	*mg. per cent*	*per cent*	*gm.*
17	39	m	cardiac insufficiency	190/130	1 month	1 month of dyspnea, edema, nocturia and ascites. Decompensation.	..	..	..	660
18	39	f	"	210/170	7 years	7 years of high blood pressure. 1 month of dyspnea, cough, cyanosis and edema. Decompensation.	..	60	..	580
19	50	m	"	175/105	1 year	1 year of angina pectoris, dyspnea and pleural effusion. Decompensation.	..	..	..	760
20	54	m	"	162/120	1 year	1 year of high blood pressure, dyspnea, cough, edema and nocturia. Decompensation.	..	..	..	860
21	55	m	"	240/160	2 years	2 years of nocturia, dyspnea weakness and epistaxis. 6 weeks of palpitation and edema. Decompensation.	..	50	..	560
22	55	f	"	240/130	3 years	3 years of headache, blurred vision, palpitation, praecordial pain, edema and nocturia. Decompensation.	23.30	..	..	500
23	56	m	"	160/115	5 years	5 years of cough and epistaxis. 3 weeks of edema and dyspnea. Decompensation.	..	..	..	560

TABLE I (*continued*)

Coronary sclerosis	Mural thrombosis	Weight of kidneys	Sclerosis small and medium-sized renal arteries	Sclerosis of renal afferent arterioles	Tubular atrophy	Glomeruli						
						Non-Hypertensive			Hypertensive contracted			Hyaline
						No inflam.	Focal inflam.	Diffuse inflam.	No inflam.	Focal inflam.	Diffuse inflam.	
		gm.				*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
–	absent	320	–	–	–	65	..	..	15	..	..	20
++	absent	290	++	++	+	75	..	..	15	..	..	10
++	absent	320	–	–	–	91	..	..	4	..	..	5

TABLE II

Essential Hypertension (Cardiac Group)

Coronary sclerosis	Mural thrombosis	Weight of kidneys	Sclerosis small and medium-sized renal arteries	Sclerosis of renal afferent arterioles	Tubular atrophy	Glomeruli						
						Non-Hypertensive			Hypertensive contracted			Hyaline
						No inflam.	Focal inflam.	Diffuse inflam.	No inflam.	Focal inflam.	Diffuse inflam.	
		gm.				*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
+++	present	370	++	+	–	70	..	..	25	..	..	5
+	absent	290	++++	++++	++	34	1	1	46	2	2	14
+++	present	300	+++	+	+	47	2	4	37	..	..	10
?	absent	520	+	+	–	55	..	..	15	..	..	30
+++	absent	220	++++	++++	++	18	3	2	73	1	..	3
++	absent	270	++	+	+	42	..	..	40	..	..	18
–	absent	270	++	+	–	80	..	..	8	..	..	12

TABLE II (*continued*)

Case number	Age	Sex	Cause of death	Blood pressure	Known duration of symptoms	Summary of history	Blood urea nitrogen	Blood non-protein nitrogen	Urine phenol sulpho-neph-thalein	Heart weight
	years			*mm. mercury*			*mg. per cent*	*mg. per cent*	*per cent*	*per cent*
24	56	m	cardiac insufficiency	180/120	12 years	12 years ago two cerebral accidents. At that time, blood pressure 128/80, dizziness, dyspnea, edema and nocturia. 4 years ago blood pressure 170/80, headaches, nocturia, edema and ascites. Decompensation.	..	..	35	830
25	57	f	"	150/60	4 months	4 months of dyspnea, edema and weakness. Decompensation.	..	..	..	500
26	58	f	"	252/148	3 years	3 years of dyspnea and high blood pressure. 4 months of decompensation.	..	50	..	560
27	63	m	"	200/140	11 months	11 months of decompensation.	..	..	..	850
28	63	m	"	210/110	2 years	2 years of high blood pressure. 2 years ago a cerebral accident. Now angina pectoris and decompensation.	..	..	..	515
29	64	m	"	170/110	4 years	4 years of dyspnea, cough, nocturia and edema. Decompensation.	..	..	..	475
30	70	f	"	200/130	18 months	18 months of dyspnea. 1 month of angina pectoris and fibrillation.	..	..	..	520
31	70	f	"	200/?	9 months	9 months of weakness and dyspnea. 2 weeks of ascites and cyanosis. Decompensation.	..	..	..	520
32	74	m	"	140/80	6 years	6 years of dyspnea, edema and angina pectoris. Decompensation.	..	..	..	600
33	80	m	"	170/95	7 weeks	7 weeks of dyspnea, weakness, dizziness and edema. Decompensation.	..	45	..	600
34	80	f	"	160/110	9 years	9 years ago a cerebral accident. 5 years ago another. Decompensation.	..	..	..	400
35	82	m	"	170/110	3 months	3 months of edema and cyanosis. Tortuous retinal arteries. Decompensation.	..	82	..	750

TABLE II (*continued*)

Coronary sclerosis	Mural thrombosis	Weight of kidneys	Sclerosis small and medium-sized renal arteries.	Sclerosis of renal afferent arterioles	Tubular atrophy	Glomeruli						
						Non-Hypertensive			Hypertensive contracted			Hyaline
						No inflam.	Focal inflam.	Diffuse inflam.	No inflam.	Focal inflam.	Diffuse inflam.	
		gm.				*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
++++	present	310	+++	++++	+	52	..	..	30	..	..	18
++	absent	185	++++	++++	++++	26	2	10	10	..	..	52
–	absent	small	++++	++++	++++	38	2	1	20	8	1	30
+	absent	410	++	+	+	68	..	..	18	..	..	14
++++	absent	240	++++	++++	++++	10	3	4	66	2	..	15
+	absent	310	+	+	+	57	..	..	23	..	..	20
++++	present	380	+	+	–	72	..	..	13	..	..	15
+++	absent	400	++	+	–	83	..	..	9	..	..	8
++++	absent	320	++	+	–	76	..	..	12	..	..	12
++	absent	400	++	+	–	75	..	..	17	..	..	8
++++	present	400	++	++	–	66	..	..	30	..	..	4
–	absent	290	++++	++	+	35	..	2	48	2	2	11

TABLE III

Essential Hypertension (Renal Group)

Case number	Age	Sex	Cause of death	Blood pressure	Known duration of symptoms	Summary of history	Blood urea nitrogen	Blood non-protein nitrogen	Urine phenol sulphonephthalein	Heart weight
	years			*mm. mercury*			*mg. per cent*	*mg. per cent*	*per cent*	*gm.*
36	34	f	uremia	280/150	3 years	3 years of headaches, dizziness, blurring of vision and epistaxis. Fundi show old hemorrhages. Uremia.	37.78	..	..	480
37	37	f	"	220/120	1 year	1 year of epistaxis, failing vision, polyuria, dyspnea and palpitation. 3 months of headache, edema and praecordial pain. Fundi show recent and old hemorrhages. Uremia.	58.26	..	0	542
38	46	m	"	227/140	3 months	3 months of praecordial pain, dyspnea dizziness, edema, nocturia and vomiting. Albuminuric retinitis. Uremia.	..	193	0	470
39	47	m	"	245/160	7 years	7 years of headaches, weakness and nocturia. 3 years of high blood pressure and impaired vision. Dyspnea and edema. Uremia.	200.4	..	23	775
40	50	f	"	260/?	3 years	3 years of high blood pressure, dyspnea, headaches and nocturia. 2 years ago a cerebral accident. Uremia.	..	111	..	485
41	50	m	"	high	3 years	3 years of heart trouble. A few weeks of dyspnea, cyanosis, edema and vomiting. Uremia.	..	..	..	640
42	52	m	"	240/150	1 year	1 year of high blood pressure, weakness, dyspnea and epistaxis. Cerebral accident with facial paralysis. Uremia.	..	135	20	570
43	53	m	"	208/126	3 years	3 years of palpitation, epistaxis and nocturia. 6 weeks of cough, dyspnea and praecordial pain. Fundi show exudate and old hemorrhages. Uremia.	135	..	..	520
44	57	m	"	236/144	6 years	6 years of nocturia. 8 months of headache, blurred vision, epistaxis, dyspnea and weakness. Fundi show old hemorrhages. Uremia.	69	..	..	510
45	57	m	"	230/170	3 years	3 years of high blood pressure, dyspnea, praecordial pain, nocturia and edema. Months of chronic uremia.	..	166	0	555
46	58	m	"	230/160	3 years	3 years ago a cerebral accident. Since then, angina pectoris, headaches, dyspnea, edema and chronic uremia. Fundi show new and old hemorrhages.	..	243	0	660
47	60	m	"	208/178	?	Semi-comatose with clinical uremia.	..	..	..	590
48	69	f	"	200/110	6 months	6 months of angina pectoris, weakness, palpitation and dyspnea. Fundi show old hemorrhages. Uremia.	..	300	..	390
49	71	m	"	high	2 weeks	2 weeks of cough, weakness, cyanosis, delirium and twitching. Uremia.	..	75	..	435

TABLE III

Essential Hypertension (Renal Group)

Coronary sclerosis	Mural thrombosis	Weight of kidneys	Sclerosis small and medium-sized renal arteries	Sclerosis renal afferent arterioles	Tubular atrophy	Glomeruli						
						Non-Hypertensive			Hypertensive contracted			Hyaline
						No inflam.	Focal inflam.	Diffuse inflam.	No inflam.	Focal inflam.	Diffuse inflam.	
		gm.				*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
++	absent	200	++++	+++	+++	25	2	2	62	6	1	2
++	absent	215	++++	++++	++++	46	..	..	66	3	2	23
?	absent	110	++++	++++	++++	..	..	..	27	3	..	70
+	absent	150	++++	++++	++++	4	2	1	47	2	4	40
–	absent	100	++++	++++	++++	10	8	..	44	5	..	33
+	absent	380	++++	+++	++++	20	10	2	7	6	..	55
+++	absent	300	++++	++++	++++	15	2	2	52	8	3	18
+	absent	165	+++	++++	++++	20	4	..	27	1	7	41
++	absent	285	++++	++++	++++	34	..	..	55	4	..	7
?	absent	195	++++	++++	++++	..	..	..	76	4	..	20
+++	absent	220	++++	++++	++++	14	1	..	46	5	1	33
–	absent	150	++++	++++	++++	6	1	..	8	9	3	73
+++	absent	80	++++	++++	++++	20	8	..	18	5	11	38
+	absent	288	++++	++++	+++	20	1	2	64	1	2	10

TABLE IV

Essential Hypertension (Miscellaneous Group)

Case number	Age	Sex	Cause of death	Blood pressure	Known duration of symptoms	Summary of history	Blood urea nitrogen	Blood non-protein nitrogen	Urine phenol sulpho-neph-thalein	Heart weight
	years			*mm. mercury*			*mg. per cent*	*mg. per cent*	*per cent*	*gm.*
50	47	m	rupture of aorta	242/140	6 years	6 years of headaches and dyspnea. 1 year of high blood pressure and edema. 3 days of acute abdominal pain.	..	..	..	1280
51	56	m	diabetes	208/104	several years	Diabetes for years. Admitted in coma and died in 3 days.	..	33	..	770

TABLE V

Control Group (Kidneys from Non-Hypertensives in the 5th, 6th, 7th and 8th Decades)

Case number	Age	Sex	Cause of death	Blood pressure	Heart weight	Coronary sclerosis	Mural thrombosis	Weight of kidneys
	years			*mm. mercury*	*gm.*			*gm.*
N 1	42	m	carcinoma stomach	120/80	255	–	absent	305
N 2	45	f	carcinoma breast	112/76	small	–	"	300
N 3	54	m	pulmonary tuberculosis	normal	340	–	"	480
N 4	55	m	carcinoma esophagus	105/75	260	–	"	380
N 5	58	m	chronic lymphatic leukemia	120/80	300	–	"	360
N 6	60	f	perforated gastric ulcer	normal	260	–	"	280
N 7	60	m	carcinoma esophagus	104/72	290	–	"	275
N 8	70	m	lobar pneumonia	110/80	310	–	"	250
N 9	80	f	mitral stenosis with decompensation	120/90	320	–	"	210

TABLE IV

Essential Hypertension (Miscellaneous Group)

Coronary sclerosis	Mural thrombosis	Weight of kidneys	Sclerosis small and medium-sized renal arteries	Sclerosis of renal afferent arterioles	Tubular atrophy	Glomeruli						
						Non-Hypertensive			Hypertensive contracted			Hyaline
						No inflam.	Focal inflam.	Diffuse inflam.	No inflam.	Focal inflam.	Diffuse inflam.	
		gm.				*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
?	absent	490	++++	++++	+++	18	..	2	67	4	..	9
++++	absent	455	++	++	+	68	..	..	22	..	..	10

TABLE V

Control Group (Kidneys from Non-Hypertensives in the 5th, 6th, 7th and 8th Decades)

Sclerosis of small and medium-sized renal arteries	Sclerosis of renal afferent arterioles	Tubular atrophy	Glomeruli						
			Non-Hypertensive			Hypertensive contracted			Hyaline
			No inflam.	Focal inflam.	Diffuse inflam.	No inflam.	Focal inflam.	Diffuse inflam.	
			per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
–	–	–	98	..	..	..	..	..	2
–	–	–	95	..	..	..	..	..	5
–	–	–	95	..	..	..	..	..	5
+	–	–	100	..	..	..	..	..	..
–	–	–	94	..	..	3	..	..	3
–	–	–	91	..	..	2	..	..	7
+	–	–	97	..	..	..	..	..	3
+	–	–	92	..	..	2	..	..	6
++	–	–	92	..	..	..	..	..	8

No one of the fifty-one cases happened to have the acute inflammatory arteritis described by Fahr or the arteriolar necrosis with glomerular infarction seen by Bell and Clawson. Inflammatory

TABLE VI

Summary of Glomerular Lesions

	Number of cases	Average age	Non-Hypertensive glomeruli	Hypertensive contracted glomeruli	Hyaline glomeruli
		years	*average per cent*	*average per cent*	*average per cent*
Non-hypertensive control group	9	58	96.2	0.8	4
Essential hypertension cerebral group	16	59	63	24	13
Essential hypertension cardiac group	19	55	52	33	15
Essential hypertension miscellaneous group	2	51	44	48	8
Essential hypertension renal group	14	52	20	47	33

glomeruli in my series usually have arterioles with a very marked degree of sclerosis or thrombosis extending up to or through the hilum.

Table V shows that there is no arteriolosclerosis in the control group. Two of the cerebral group also show no arteriolosclerosis (Table I, cases 14 and 16) although they have a small percentage of hypertensive glomeruli. This discrepancy may be due to the relative size of glomeruli and arterioles, the former being easier to find than the latter.

The interlobular, small and medium-sized arteries of the kidneys show the changes described by others, namely, intimal atherosclerosis and hyperplastic elastic tissue intimal thickening. As noted in Table V, four of the control series have a mild degree of this sclerosis.

DISCUSSION

The glomeruli in essential hypertension are usually described as normal. In my series of fifty-one cases the renal group averages only 20 per cent normal glomeruli, the miscellaneous group 44 per cent, the cardiac group 52 per cent and the cerebral group 63 per cent. Nine non-hypertensive controls from the fifth, sixth, seventh and eighth decades average 96.2 per cent normal glomeruli (Figs. 1 and 3).

All fifty-one cases show the presence of a typical glomerulus with a thickened wrinkled basement membrane (Figs. 2 and 4). The average percentage of such glomeruli is 48 in the renal and miscellaneous groups, 31 in the cardiac group and 25 in the cerebral group. In all except Case 16 these hypertensive contracted glomeruli are present in sufficient numbers to indicate the diagnosis. It is interesting that this case according to the data available is undoubtedly primary hypertension and yet there is no cardiac hypertrophy and no arteriolosclerosis.

Hypertensive contracted glomeruli are most numerous in kidneys with extensive arteriolosclerosis (Tables I, II, III and IV). Microscopically either lesion may be considered indicative of clinical hypertension. In early cases it is simpler to look for hypertensive glomeruli than for arteriolar disease.

The thickening of the glomerular basement membrane may be the result of a spasm of the tuft or of atrophy due to ischemia or to partial disuse. Serial sections show that sclerosed arterioles may lead to normal glomeruli but that hypertensive glomeruli always have narrowed arterioles. These two facts suggest that the arteriolar lesion precedes and is related to the glomerular change. The portion of the afferent vessel close to the hypertensive glomerulus is usually normal. The subendothelial hyaline deposit with its resultant narrowing of the lumen is some distance from the glomerulus.

There are all transitions from normal to hypertensive hyaline glomeruli.

Bell [23] has described a diffuse thickening of the basement membrane in all the glomeruli in three cases of lipoid nephrosis. There was no hypertension, no tubular atrophy and no arteriosclerosis. Evidently a glomerular basement membrane thickening need not be secondary to vascular disease. The glomeruli in such a type of lipoid nephrosis are normal in size and lobulation, in contrast to the glomeruli of hypertension which are small with a decreased number of loops. Also, in these three cases of lipoid nephrosis the basement membrane of *all* the glomeruli is involved while in hypertension the percentage varies.

The glomerular tuft may be thought of as a filter with the glomerular basement membrane as the gel lying between endothelium and epithelium. The greatly increased thickness of the gel in hypertensive glomeruli must alter its permeability. This change may explain the urinary albumin in such cases.

Inflammatory glomeruli (Fig. 5) may occur in all types of essential hypertension and it is not justifiable to separate benign (without renal insufficiency) and malignant (with renal insufficiency) on such lesions. However, the greatest number of inflammatory glomeruli is found in the renal group (Table III) and a high percentage is usually indicative of a uremic death. All cases in the uremic group of this series show glomeruli with inflammatory lesions. The changes in these glomeruli are considered inflammatory rather than vascular in origin because they are generally identical with the intracapillary lesions of glomerulonephritis.

It has been suggested by others that the younger patients dying of essential hypertension have a greater number of inflammatory glomeruli. My series does not support such a view, for Cases 47 and 48, aged 60 and 69 years respectively, have the greatest inflammatory change. Neither is the highest percentage of hypertensive contracted glomeruli found in younger cases. Cases 21 and 49 who were 55 and 71 years of age have the greatest number of such glomeruli. There are not sufficient data available to determine the correlation between duration of symptoms and percentage of hypertensive glomeruli.

The renal group of essential hypertension has much in common clinically and microscopically with those cases of chronic glomerulonephritis which have severe vascular disease. Death is from uremia in both conditions and microscopically both show arteriolosclerosis and inflammatory glomeruli. However, in the kidney of chronic glomerulonephritis almost all the glomeruli are diffusely inflamed, while there are rare hypertensive and practically no normal glomeruli. On the other hand, the renal hypertensive kidney has a small number of diffusely inflamed glomeruli, a larger number with focal lesions, a high percentage of hypertensive glomeruli and a definite proportion of normal glomeruli. An anilin blue stain shows that glomerulonephritis is an intracapillary obstruction of the tufts while essential hypertension is a change in the glomerular basement membrane.

Conclusions

1. The glomerular lesion of essential hypertension is as typical as the arteriolar lesion. It consists of a decrease in size and a simplification of the glomerulus with a marked thickening and wrinkling of the glomerular basement membrane.

In this series of fifty-one cases, the average percentage of such glomeruli is 47 in the renal group (death from uremia), 33 in the cardiac group (death from myocardial insufficiency or coronary disease), and 24 in the cerebral group (death from apoplexy).

2. The arteriolosclerosis precedes and is related to the change in the glomerular basement membrane.

3. Kidneys from individuals dying in the fifth, sixth, seventh and eighth decades with a history of normal blood pressure show 96.2 per cent normal glomeruli. A rare hypertensive contracted glomerulus may be found.

4. There are inflammatory glomeruli in any type of essential hypertension but they are most numerous in the renal group. The lesions are usually focal and as many as 15 per cent of the glomeruli may be involved.

5. Anilin blue (Mallory-Heidenhain azan carmine) is recommended as a routine stain for kidney tissue. It is particularly helpful to differentiate the renal group of essential hypertension from those cases of chronic glomerulonephritis which have extensive vascular disease.

NOTE: I am indebted to Dr. F. B. Mallory for suggestions and criticism and also for the photomicrographs.

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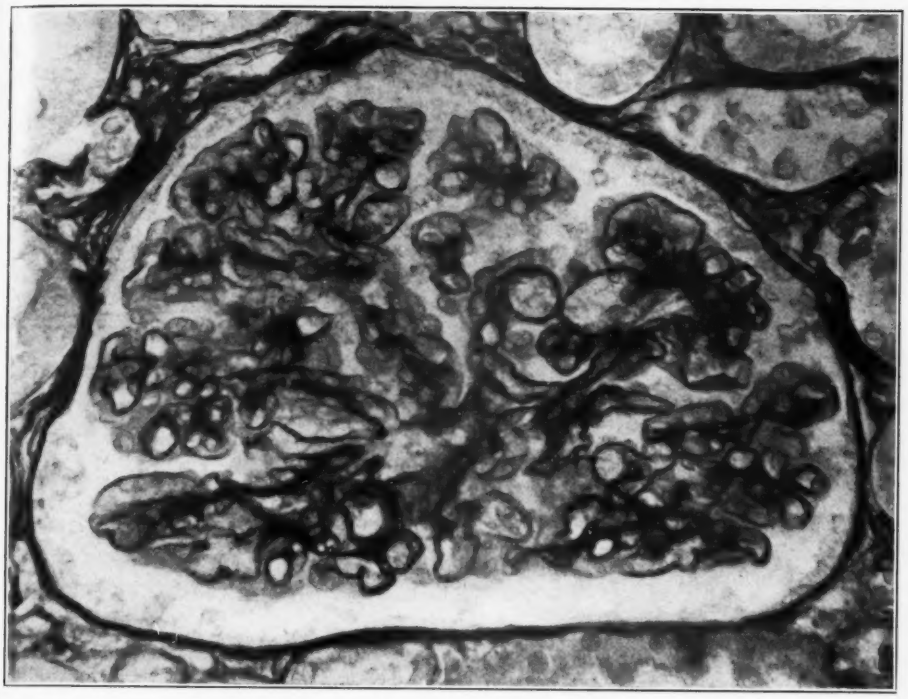
DESCRIPTION OF PLATES

PLATE 75

FIG. 1. A normal glomerulus from Case 49. Essential hypertension with death from uremia in a man of 71 years. Only 20 per cent of his glomeruli were normal. The photomicrograph shows (1) the normal thinness and continuity of the glomerular basement membrane which forms the middle layer of the wall of the tuft, (2) the continuous layer of glomerular epithelium lying external and adjacent to the membrane, and (3) a few endothelial cells lining the internal surface of the membrane. Stain, Mallory-Heidenhain azan carmine. × 500.

FIG. 2. A hypertensive contracted glomerulus from Case 37. Essential hypertension with death from uremia in a woman 37 years of age. Seventy-one per cent of her glomeruli were of this type. The photomicrograph shows (1) a small simplified glomerulus with many less loops than normal, and (2) a marked thickening and wrinkling of the glomerular basement membrane. Stain, Mallory-Heidenhain azan carmine. × 500.



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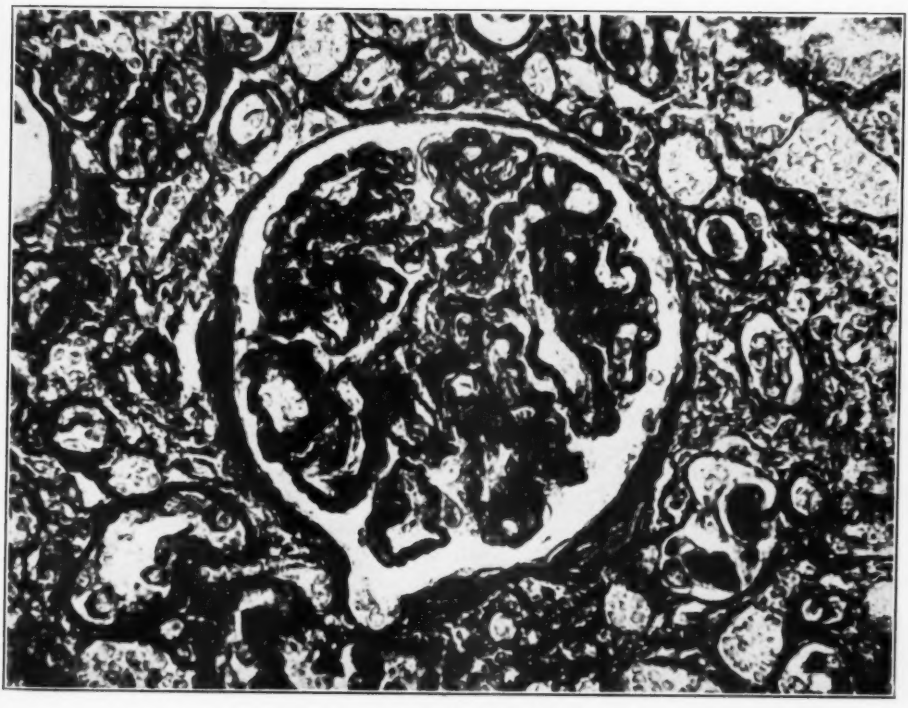


2

McGregor Renal Glomerulus in Essential Hypertension

PLATE 76

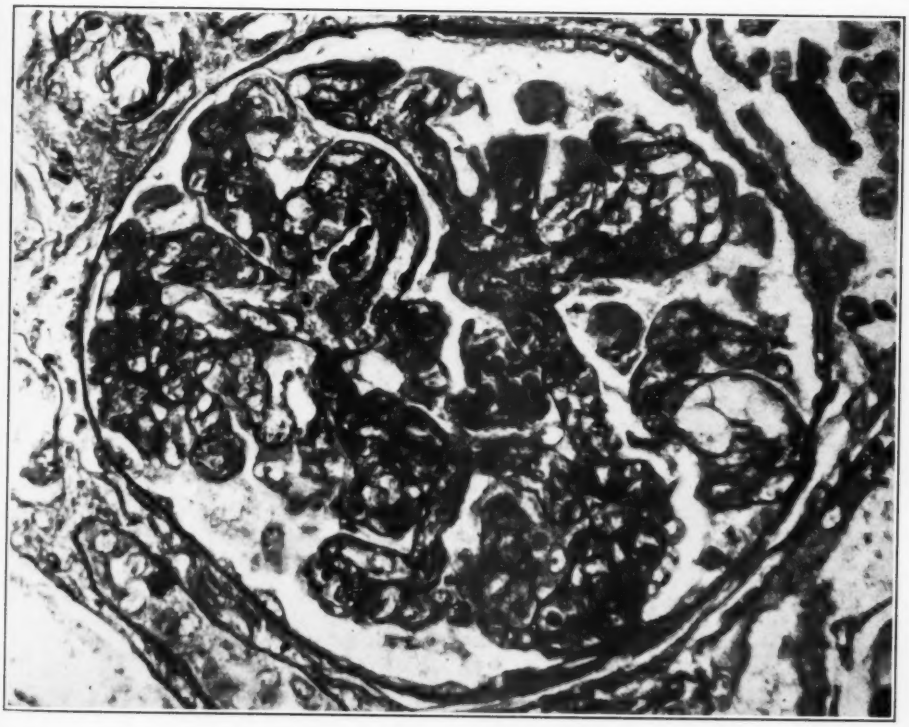
FIG. 3. Two normal loops from a normal glomerulus. Case 50. Essential hypertension with death from rupture of the aorta in a man 47 years of age. Only 18 per cent of his glomeruli were normal. The photomicrograph shows (1) the thinness of the normal glomerular basement membrane, and (2) the continuous covering layer of glomerular epithelial cytoplasm. There are four nuclei in the field of which the upper one and the lower two are external to the basement membrane and are epithelial. The fourth nucleus which lies in the center of the group is internal to the basement membrane and is endothelial. Stain, Masson's rapid method with iron hematoxylin substituted for the azo carmine in the Mallory-Heidenhain azan carmine technique. × 1500.

FIG. 4. Two loops from a hypertensive contracted glomerulus. Case 50 (same as Fig. 3). Essential hypertension with death from rupture of the aorta in a man 47 years of age. Seventy-one per cent of his glomeruli were of the type in this illustration. The photomicrograph shows (1) a marked thickening and wrinkling of the glomerular basement membrane (contrast with Fig. 3), (2) normal glomerular epithelium external to the membrane, and (3) normal glomerular endothelium internal to the membrane. Stain, the same as in Fig. 3. × 1500.

FIG. 5. A glomerulus showing diffuse acute inflammation. Case 21. Essential hypertension with death from cardiac decompensation in a man 55 years of age. Only 2 per cent of such glomeruli were found. The photomicrograph shows (1) an enlarged glomerulus, (2) glomerular epithelium which is swollen and undergoing hyaline granular degeneration, (3) a glomerular basement membrane of normal thinness, and (4) obstruction to the circulation by intracapillary fibers and proliferated endothelium. The loops on the right contain mononuclear cells filled with fat. (5) In the upper left portion of the field, an arteriole with an irregular subendothelial deposit of hyalin is seen. Stain, the same as in Fig. 3. × 500.

3

4



5

A CASE OF LYMPHOBLASTOMA, HODGKIN'S DISEASE AND TUBERCULOSIS *

H. E. MacMahon, M.D., and F. Parker Jr., M.D.

(From the Pathological Laboratory of the Boston City Hospital, Boston, Mass.)

In recent years the study of tumors of the lymphatic system has received unusually widespread attention both in regard to etiology and classification. Many types have been described, usually however in an uncomplicated form, but occasionally associated with tuberculosis or tumors of another kind. A case of aleukemic lymphatic leukemia that later developed lymphatic leukemia, and at autopsy showed in addition Hodgkin's disease and tuberculosis, forms the basis for this report.

Richter [1] recently reported a case of generalized reticulum cell sarcoma of the lymph nodes associated with lymphatic leukemia. The patient, a male 46 years of age, entered the hospital with enlarged cervical lymph nodes which had been present about seven weeks. His red blood cell count was 3,700,000, and he had a leucocytosis of 98,400, 90 per cent of which were lymphocytes. His condition became progressively worse and he died about three weeks after admission. At the time of death the reticulum cell sarcoma was the more actively growing lesion, but the wide distribution and relative quiescence of the leukemic foci indicated the long and probably earlier existence of the latter.

Still more recently Flashman and Leopold [2] reported a case in an elderly male beginning with a primary retroperitoneal lymphosarcoma and terminating with leukemia. Tissue obtained by biopsy from the inguinal lymph nodes that had been enlarged for twelve months revealed a lymphosarcoma. The patient was given a long series of Roentgen-ray treatments lasting over four months. The blood picture remained unchanged till the last week or two of these treatments when the white count rose to 96,000 cells per cmm., with 90 per cent small lymphocytes. The patient lived three weeks longer, and during that time the white blood count rapidly in-

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creased to 444,000 cells per cmm., with a differential count showing 90 to 96 per cent small lymphocytes.

It is not necessary to review again the literature relating to tumors of the lymphatic apparatus associated with leukemias since this has been adequately covered by Flashman and Leopold, who in addition have included an excellent bibliography.

Report of Case

Clinical History: R. J. W., a white male, aged 61 years, steeplejack by occupation, entered the medical wards of the Boston City Hospital on November 23, 1925, complaining of distention of the abdomen, swelling of the right leg and the left ankle, and enlargement of the inguinal group of lymph nodes.

Present Illness: The patient was in moderately good health until about eight weeks prior to entry, when he first noticed swelling of his abdomen. About three weeks later his right leg became red and began to swell, and a week or two after this he noticed a similar swelling of his left ankle. He was indefinite about the duration of the enlarged nodes in the groin, but realized they had been present for several weeks.

Past History: He had recurrent attacks of bleeding hemorrhoids for eighteen years previous to an operation April 12, 1923. At this time the surgical records indicate that he had a chain of small discrete non-tender lymph nodes above Poupart's ligament on both sides. His past history was otherwise entirely negative.

Physical Examination: There was an enlargement of all superficial lymph nodes; this was particularly noticeable in the inguinal regions. The abdomen was distended but there was neither shifting dullness nor a fluid wave. An indefinite mass was felt in the left upper quadrant that was thought to be the spleen. The right leg and thigh were edematous and reddened; the left leg was edematous to the knee.

The rest of the physical examination including an X-ray of the chest revealed no further positive findings.

Laboratory Examination: The white blood cell count was 11,600 with 44 per cent lymphocytes; the red blood cells, 4,728,000, and the hemoglobin 75 per cent.

On November 27, 1925, four days after admission, the first biopsy tissue from a node removed from the left axilla was diagnosed as a "slowly growing lymphoblastoma."

Report on First Biopsy Specimen

The specimen (S25–2670) consists of an encapsulated lymph node about 2 cm. in diameter. The fresh surface is homogeneous, dull, white and gelatinous.

Microscopically, in one or two areas the normal markings are entirely obliterated by a homogeneous diffuse growth of lymphocytes. Elsewhere the lymphocytes are growing in rather densely

packed nodules and cords without differentiated germinal centers. There is fusion of both nodules and cords, infiltration of both pulp and capsule and almost complete obliteration of the sinuses.

The cells resemble small mature lymphocytes. There are a few lymphoblasts and a few polymorphonuclear leucocytes, including an occasional eosinophile.

Progress Note: The patient's condition was unchanged for about ten days and on December 5, 1925, a second lymph node was obtained for microscopic examination and diagnosed "hyperplasia of lymphoid tissue."

Report on Second Biopsy Specimen

The specimen (S25–2753) consists of a small, soft, red, irregular piece of tissue 2 by 1 by 1 cm.

This lymph node has many normal-appearing nodules, with well differentiated germinal centers composed of large young lymphocytes, and lymphoblasts in which mitoses are numerous. As in the previous biopsy both stroma and capsule are infiltrated with small mature lymphocytes, but the sinuses are not obliterated, and here and there one is distended with mature lymphocytes.

Progress Note (Continued): During the succeeding four weeks the patient received four X-ray treatments. The edema and redness of the legs disappeared but the abdomen remained distended. The white blood count varied from 14,100 on December 12, 1925, to 5,600 on December 22, 1925, with an average throughout of 50 per cent lymphocytes. While in the hospital his weight fell from 158 to 144 pounds. On January 6, 1926 he was discharged feeling better and relatively free from symptoms.

On March 25, 1927 he reëntered the hospital for the second time, after being out just a little more than a year, but in the interval he was kept under observation in the out-patient department. He was fairly well until two weeks before this second admission when his abdomen became more distended, and the swelling of his legs, which had returned somewhat soon after he left the hospital, became more marked at about this time; he also developed shortness of breath on exertion.

A physical examination showed marked distention of the abdomen, shifting dullness and a fluid wave. There was general lymph node enlargement as before, but the nodes in the inguinal region were larger. His spleen was readily palpable.

The white blood count showed 59,000 cells per cmm., 92 per cent of which were lymphocytes.

The abdomen was tapped and 4000 cc. of chylous fluid were withdrawn, and for several days this fluid continued to drain away.

On April 30, 1927, an infection developed in a lymph node in his left groin; this progressed for several days causing a fever which went as high as 102° and

103° F. On May 5, the node was incised and drained, and in forty-eight hours the temperature returned to normal.

At this time, the blood picture changed, and a count taken on May 13 showed only 10,000 white blood cells, and of these only 22 per cent were lymphocytes.

He remained in the hospital almost three months, and on June 6, 1927 when he was discharged he felt much better. The swelling of the legs had disappeared but there was still a moderate degree of ascites.

Three months more elapsed until he was readmitted on September 9, 1927, for the third time. After leaving the hospital in June he spent most of his time camping in the woods and was fairly free from symptoms till August when his ankles began to swell, and the edema gradually extended toward the body. His abdomen became more distended, the genitals were swollen and he once again developed shortness of breath.

A physical examination on his third admission again revealed considerable edema of both legs and scrotum, and marked distention of the abdomen. The blood picture at this time showed 11,000 white blood cells, with 34 per cent lymphocytes, 59 per cent polymorphonuclear leucocytes and 7 per cent monocytes.

On September 16, 1927, that is, one week after admission, his abdomen was tapped and 15,000 cc. of chylous fluid were withdrawn. An examination of this fluid showed 160,000 lymphocytes per cmm., and this high cell count was considered an adequate cause for the turbidity of the fluid.

Roentgen-ray therapy was started almost immediately, but the patient's condition grew worse, he became dyspneic and developed râles at both bases.

On November 11, 1927, an axillary lymph node was removed for biopsy and the microscopic diagnosis "suggested chronic inflammation rather than tumor but a positive diagnosis was not possible."

Report of Third Biopsy Specimen

The specimen (S27–2637) is a small, moderately firm, encapsulated lymph node about 2 cm. in diameter.

Microscopically this lymph node resembles the second biopsy specimen. The normal architecture of the node in places is well preserved, and there are many normal lymph nodules with well differentiated germinal centers. In addition there are other nodules composed of solid masses of uniformly mature lymphocytes. The capsule, pulp and trabeculae are infiltrated with lymphocytes, but the peripheral sinus is quite patent.

Progress Note (Continued): On November 18, 1927, he was again tapped and 5000 cc. of chylous fluid were withdrawn. About a week later another series of X-ray exposures was begun, each of which was followed by twenty-four hours of vomiting and diarrhoea. On December 16, 1927, a fourth lymph node was removed for examination and this was diagnosed "lymphoblastoma."

Report on Fourth Biopsy Specimen

The specimen (S27–2970) is a soft irregular piece of tissue 2 by 1 by 1 cm.

Microscopically, the normal architecture is obliterated by a diffuse growth of mature lymphocytes. The capsule is thinned and infiltrated with lymphocytes. There are no distinct lymph nodules, and only in a few places can the peripheral sinus still be made out. There is an occasional large tumor giant cell of the so-called Sternberg or Dorothy Reed type.

Progress Note (Continued): Soon after the last series of Roentgen-ray treatments was started he began steadily to improve.

In the latter part of January 1928 the ascites had almost cleared up and he was up and about the ward most of the time. Five or six months passed with little or no change before the lymph nodes in the inguinal region began to enlarge, and his abdomen again began to fill, but repeated blood counts taken throughout this time showed a normal number of white blood cells and normal differential values.

From about the first of August until the patient's death in September, the general condition grew progressively worse. The abdomen continued to fill and the resulting ascites had to be relieved on several occasions. His appetite diminished, he lost considerable weight and on September 8, 1928, just about three years after his first admission, he died.

Summary of Clinical History

A male, 61 years of age, entered the hospital with some abdominal distention, palpable superficial lymph nodes, a normal total white blood count, but with a relatively high lymphocyte value of 44 per cent. A biopsy specimen taken at this time was diagnosed lymphoblastoma of the type consistent with aleukemic leukemia.

After an interval of about a year and a half the patient was readmitted, again showing abdominal distention and general lymph node enlargement. At this time, the white blood count was about 60,000 cells per cmm., with 90 per cent lymphocytes, and the case was diagnosed "lymphatic leukemia." He had been in the hospital only about six weeks when an acute lymphnoditis developed in one of his inguinal lymph nodes. He became acutely ill and his temperature rose to 103° F. The node was drained and after forty-eight hours he felt better and his temperature returned to normal.

At this time his white blood count was only 10,000, and his differential count taken repeatedly was normal. More than a year

elapsed after this before the patient died and never during this time did the normal total and differential count show an appreciable variation.

Clinical Diagnosis: Aleukemic leukemia with reversal of white blood cell count.

Autopsy Report

An autopsy (A28–319) was performed on September 8, four hours postmortem. The body is poorly developed and emaciated. The abdomen is distended and fluctuant and the lower extremities are considerably edematous. Both axillary and inguinal lymph nodes are palpable bilaterally. There is very little subcutaneous fat and the pectoral and abdominal muscles are atrophic.

Peritoneal Cavity: The surfaces are dull, rather opaque, and roughened by fine sand-like granulations. A thin fibrinous exudate covers the capsule of both spleen and liver. The cavity contains 4000 cc. of milk-like fluid. The mesenteric and iliac lymph nodes are greatly enlarged. The spleen is larger than normal, roughened and bound to the diaphragm by old fibrous adhesions.

Pleural Cavities: The left contains about 25 cc. of milk-like fluid; the right contains a similar amount, but this is watery and blood-tinged. The lower lobe of the right lung is firmly bound to the chest wall and diaphragm.

Heart: Weight 250 gm., is rather small and unusually soft. There is considerable gelatinous atrophic fat beneath the epicardium. The myocardium is smooth, homogeneous and dark brown. The endocardium and valves are negative, but the coronary arteries are moderately atheromatous.

Lungs: There are several nodules in the upper lobe of the left lung that are firm, discrete, and vary from 0.5 to 2 cm. in diameter.

Spleen: Weight 350 gm. It is rough, nodular and firm. The fresh surfaces are homogeneous and red showing no visible malpighian bodies.

Gastro-Intestinal Tract: Lying at the duodenojejunal junction is a single, firm area of chronic ulceration 2 cm. in diameter extending into and beneath the mucosa.

Pancreas: This is very deeply embedded in enlarged lymph nodes and connective tissue.

Liver: Weight 1500 gm. The capsule is loosely covered with a

delicate, lacy, fibrinous exudate. The fresh surface of the liver is reddish brown and stippled throughout with very minute fine white nodules.

Kidneys: Weight 200 gm. They are small and firm and the capsules strip from very finely granular surfaces. The cut surface is pale and the finer markings are poorly differentiated. Both pelves and ureters are slightly dilated; the latter pass directly through enlarged groups of iliac lymph nodes but are not grossly constricted in these areas.

Aorta: Superficial atheromatous ulcers are distributed throughout both thoracic and abdominal portions. The lower end of the aorta and both common iliac arteries are completely encircled by enlarged lymph nodes.

Bone Marrow: Both vertebral and femoral marrows are red.

Lymph Nodes: There is a general enlargement of the lymph nodes throughout the body, which is especially noticeable in the abdomen and pelvis. The nodes are firm, discrete, gray or grayish pink, and vary considerably in size. Some nodes show multiple minute foci of necrosis, whereas others, equally large and nearby, show minute hemorrhages but no necrosis. The largest group of nodes is in the mesentery of the small intestine; here they are adherent but quite discrete, and vary from 2 to 6 cm. in diameter. The lymphatics lying in the mesentery between the intestine and the enlarged nodes stand out as thin yellowish white lines.

Examination of Fluid in Peritoneum: The milky appearance completely clears on the addition of ether, and shaking. Smears of sediment stained both vitally and in fixed preparations show very many lymphocytes, some polymorphonuclear and endothelial leucocytes, and few desquamated mesothelial cells.

Anatomical Diagnoses: Malignant tumor of lymph nodes with metastases to liver and lung; chylous ascites; healed pleuritis; splenomegaly with chronic perisplenitis; chronic ulcer of jejunum.

Microscopic Report

Heart: The epicardium is composed largely of atrophic fat which contains several small foci of mature lymphocytes. The vessels are sclerosed and the muscle fibers show atrophy and considerable pigmentation.

Lungs: Sections taken through the nodules that in gross were considered to be tumor metastases, show old and recent tuberculous lesions. Irregular areas of necrosis are surrounded by a chronic inflammatory reaction in which are many solitary tubercles. The walls of a few of the medium-sized vessels are involved in this tuberculous process, and the lumina are almost completely thrombosed. The surrounding lung tissue is moderately atelectatic with the alveoli partially filled with fibrin and endothelial leucocytes.

Spleen: The spleen shows several different lesions. Miliary tubercles are scattered throughout the pulp. There are small discrete areas composed entirely of cells resembling those of the Hodgkin's type of tumor cell; most of these areas lie in the pulp, but occasionally they are found bulging up beneath the endothelium of the larger vessels. There are also numerous, rather discrete foci of mature lymphocytes lying beneath the endothelium of similar vessels. The connective tissue of the pulp is generally increased throughout. The endothelial cells lining the sinuses are hypertrophied and show occasional mitoses, while endothelial leucocytes within the sinuses contain both red blood cells and blood pigment. A dense layer of hyaline connective tissue covers the capsule and superimposed on this is a layer of granulation tissue containing many young tubercles.

Liver: Sections show numerous small, discrete and confluent foci of mature lymphocytes. Many of these foci are in and about portal areas while others are scattered throughout the lobules. Nowhere is there a suggestion of either compression or invasion of liver parenchyma.

Solitary and conglomerate tubercles are scattered throughout, and many of these are situated in the portal areas lying either along the margin or entirely within the nodules of lymphocytes.

There are also larger discrete areas composed of cells of the Hodgkin's type, similar to those already described in the spleen. These cells are growing rapidly and compressing and invading the surrounding parenchyma.

Owing to the presence of the masses of lymphocytes the bile ducts in the portal areas are elongated. Where much of the lymphoid tissue has disappeared, the increase in connective tissue and the elongation and apparent increase in the number of bile ducts produce a picture simulating that of healed obstructive cirrhosis.

The endothelial cells lining the sinuses are hypertrophied and unusually prominent.

Pancreas: Solitary tubercles are distributed over the peritoneal surface and within the stroma of the pancreas. There is slight sclerosis of both larger vessels and acinar tissue.

Parietal Peritoneum: This is thickened by a layer of granulation tissue containing many solitary tubercles.

Intestine: Section from the jejunum shows a chronic ulcer extending through the submucosa into the circular muscle. Miliary tubercles are scattered along the surface of the ulcer and also along the thickened serosa.

Kidney: There is moderate sclerosis of the cortical portion of the kidney with atrophy and disappearance of many of the tubules.

Adrenal: The medulla is moderately infiltrated with mature lymphocytes and collections of endothelial leucocytes are found in the cortex.

Aorta: The intima shows hyaline thickening with organization of fibrin along the surface.

Bone Marrow: Miliary tubercles and small foci of mature lymphocytes are seen in the vertebral marrow. The femoral marrow contains a considerable amount of lymphoid tissue, in addition to showing a moderate degree of hematopoiesis.

Lymph Nodes: There is a wide variation in the histological picture of the many lymph nodes examined. Not only do nodes from widely separated areas differ but also those lying side by side. Furthermore, many individual nodes show not merely one, but two, and sometimes three distinct pathological lesions. Because of the varied and unusual character of the lymphoid tissue, only a few of the most typical nodes will be described in detail.

Lymph Node 1: This node is characterized by the presence of many nodules of mature lymphocytes. The stroma and capsule are infiltrated with these cells. The medullary and peripheral sinuses contain clusters of lymphocytes as well as many phagocytic endothelial leucocytes. There are no mitoses and no tumor giant cells.

Solitary and conglomerate tubercles are distributed in the periphery.

The histological diagnosis of such a node lies between lymphoblastoma composed of mature lymphocytes, and chronic inflammation; and in either case the picture is complicated by tuberculosis.

Lymph Node 2: This node, which lay adjacent to the one just described, shows almost no lymphoid tissue. About the periphery is a zone of granulation tissue with a few tubercles and many tuberculous giant cells. The remainder of the node is composed simply of necrotic cellular débris.

The diagnosis of this node is tuberculosis with extensive necrosis.

Lymph Node 3: In this node, the normal architecture is largely replaced by a fairly homogeneous growth of mature lymphocytes. The capsule and pulp are infiltrated with lymphocytes, and the peripheral and medullary sinuses are almost obliterated. In addition, this node shows not only solitary tubercles but also an area composed entirely of large pleomorphic cells growing rapidly and invading the surrounding lymphoid tissue.

The microscopic diagnosis is probable lymphoblastoma associated with both Hodgkin's disease and tuberculosis.

Lymph Node 4: This node differs from the others so far described. Except for a few small islands of mature lymphocytes, it is composed entirely of cells that are rather uniform both in size and shape. They are smaller than the Hodgkin's cells and larger than lymphocytes. The cytoplasm is homogeneous and lightly basophilic. The nuclei vary somewhat in size, and the nuclear membrane is crinated and quite irregular. There is little chromatin and this is arranged in a delicate network throughout the nucleus. The nucleolus is strikingly prominent. Mitoses in these cells are numerous and very rarely there are multiple mitoses and large multinucleated tumor giant cells.

The type cell so closely resembles the large lymphoblast that such a node may also be classified as a lymphoblastoma, but the picture is quite different from that in which the tumor cell is the small mature lymphocyte.

Lymph Node 5: In this node the picture is still more complicated. There are no normal landmarks except a few scattered nodules of mature lymphocytes. The remainder of the node is composed of rapidly growing tumor cells which in some fields resemble Hodgkin's cells and in others lymphoblasts, but in many places the cells are all intermingled and here it is impossible to distinguish one cell from another.

Lymph Node 6: This is composed almost entirely of Hodgkin's tumor cells. Both nucleus and cytoplasm of these cells vary widely

in size, shape and staining. The nucleolus may be single or multiple and in either case it is large, deeply basophilic and very prominent. Multinucleated tumor giant cells as well as single and multiple mitoses are common. In addition, solitary tubercles are distributed among the tumor cells.

Lymph Node 7: The greater portion of this node resembles a slowly growing lymphoblastoma composed of mature lymphocytes. Invading the sinuses at one end are clusters of rather uniform cells suggesting young lymphoblasts. In another field there is a mass of Hodgkin's cells extending into the surrounding lymphocytes. Lastly, solitary and conglomerate tubercles are found in among both the Hodgkin's cells and the lymphocytes. Hence, the picture is one of lymphoblastoma, Hodgkin's disease and tuberculosis.

Microscopic Diagnoses: Lymphoblastoma; Hodgkin's disease; tuberculosis; atrophy of the myocardium; arteriosclerosis; chronic vascular nephritis.

Bacteriological Diagnoses: Fluid from the peritoneal cavity was injected into four guinea pigs. Two of these were autopsied at the end of six weeks and showed generalized tuberculosis. The remaining two died at the end of eight and ten weeks respectively showing still more widespread tuberculous lesions.

Material from one of the first guinea pigs was transferred to a second and this again was transferred further, while attempts were being made to obtain cultures of the tubercle bacillus. Finally, a culture was obtained from the fifth transfer pig. The organisms grew fairly rapidly and culturally resembled either the human or bovine type of *B. tuberculosis*. A heavy emulsion of this culture was injected intravenously in a rabbit and intraperitoneally into a guinea pig. The guinea pig died seventy-four days after inoculation and at autopsy showed extensive tuberculosis of the spleen, liver, omentum and lungs. The rabbit remained well and was killed four and one-half months after the inoculation. At autopsy, the only pathological changes found were a few small tubercles at the periphery of both lungs. Microscopically, these were tubercles of the cellular type and contained a few acid-fast bacilli.

On the basis of its virulence for guinea pigs and relative avirulence for rabbits, the organism was considered a human type of tubercle bacillus.

Discussion

This case, in some respects, is not unlike that of Richter's, and the two cases offer many problems in common. First, there is the question of whether lymphoblastoma and Hodgkin's disease should be regarded as true neoplasms; second, has the development of any one of these three lesions, namely, the lymphoblastoma composed of mature lymphocytes, that composed of large young lymphoblasts and lastly the Hodgkin's type of tumor, been dependent on the existence of either of the remaining two, or should the three types of lesions found at autopsy be considered genetically independent; third, should the aleukemic leukemia be considered the primary disease; and lastly, what relation does tuberculosis bear to the other lesions?

Histologically, the tumor composed of mature lymphocytes, which apparently involved the lymphoid tissue throughout the body, was probably the first to develop. It has a very general distribution not only in lymph nodes but also in the spleen, liver and bone marrow.

At the time of the autopsy there was almost complete cessation in the proliferation of mature lymphocytes. In lymph nodes, spleen and liver, mitoses in these cells were practically absent, and in many areas, especially in the liver, there was already considerable hyaline change. Thus, if this is to be considered a true tumor it is rapidly showing a spontaneous regression.

In regard to the large tumor lymphoblasts and Hodgkin's cells they were multiplying rapidly and invading the surrounding tissue; each produced metastases in both spleen and liver, and in many widely separated lymph nodes.

It would appear that the patient had had for some time a slowly growing chronic type of aleukemic leukemia, and that this, perhaps as the result of an additional stimulation, exerted a demand on a more primitive cell, namely the lymphoblast, and that this in turn was followed by proliferation of a still more primitive cell, the Hodgkin's cell, which, at the time of death, was showing all the signs of a very rapidly growing malignant tumor. However, such a progression of changes may only be conjectured since the possibility of complete independence can not be disproved.

The condition of an aleukemic leukemia changing to a manifest

leukemia is well recognized and is not an extremely unusual cytological finding; however, a case that shows these changes and then later develops a complete reversal of count is very much more uncommon. The presence of an acute infection has been reported as a cause for the reversal of count, and in this case, an acute lymphadenitis associated with a very severe systemic reaction might readily account for the change in the blood picture.

For years the frequent association of Hodgkin's disease with tuberculosis has been the subject of numerous papers, and Sternberg [3] as early as 1898 maintained that Hodgkin's disease and tuberculosis were caused by a common etiological agent. This problem has been carried on recently by L'Esperance,[4] who undertook to determine whether a relationship might exist between avian tuberculosis and Hodgkin's disease, and her report, though based on a relatively small series of experiments, at least suggests that the avian tubercle bacilli may be a factor in producing some of the lesions interpreted as Hodgkin's disease.

The human type of tubercle bacillus was isolated from this case, and it had probably been active in the body for some time since the areas of tuberculosis in the lungs were definitely chronic lesions of months or years duration. The tuberculous lesions in the liver, spleen and lymph nodes on the other hand resembled miliary tubercles and were of recent origin. It is possible that the tubercle bacillus may have borne some relation to the initiation of the original tumor of the lymphatic apparatus, and even more probable that it modified the subsequent cytological and histological course. However, these are simply hypotheses which still remain to be proved.

Summary

A case is described of an elderly patient who was admitted to the hospital with the diagnosis of aleukemic leukemia. He was watched over a period of three years, and during that time he developed a manifest lymphatic leukemia. Following a short but severe infection, his white blood count and differential values returned to normal and remained unchanged till his death a year and a half later. He came to autopsy, and examination showed that he had not only aleukemic leukemia, but also Hodgkin's disease and generalized tuberculosis.

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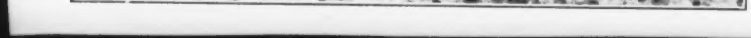
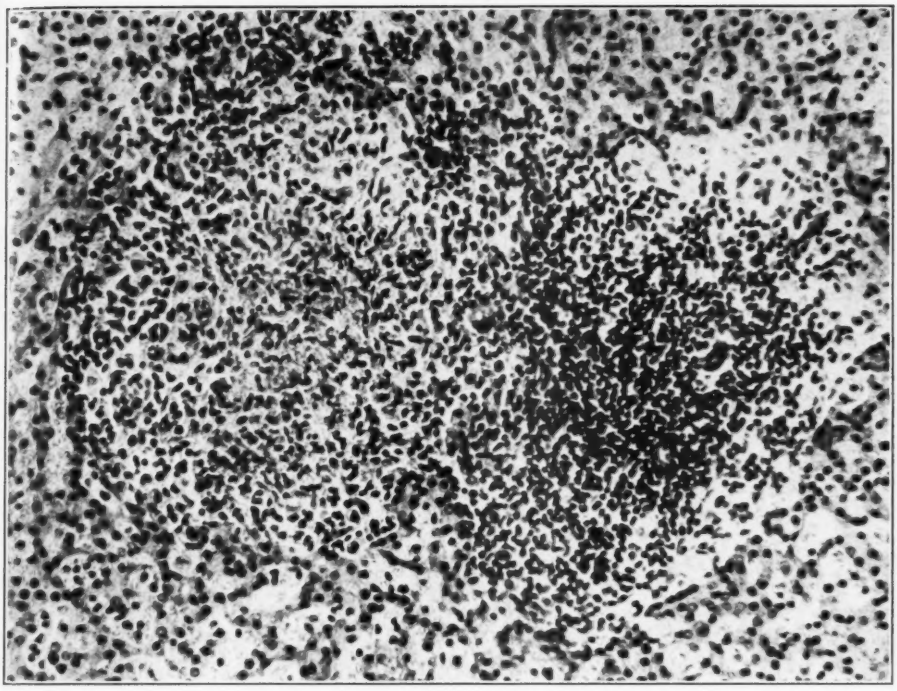
DESCRIPTION OF PLATES

PLATE 77

FIG. 1. Liver. On the left is a tubercle, and on the right a periportal leukemic infiltration. The cells of the latter are small, adult lymphocytes. × 250.

FIG. 2. Lymph node. On the left is a tubercle with a Langhan's giant cell in the center. On the right is an area of Hodgkin's disease. This area consists of large cells with irregularly shaped nuclei with prominent chromatin, and of small lymphocytes. Between the two types of lesions is a band of small lymphocytes. × 250.





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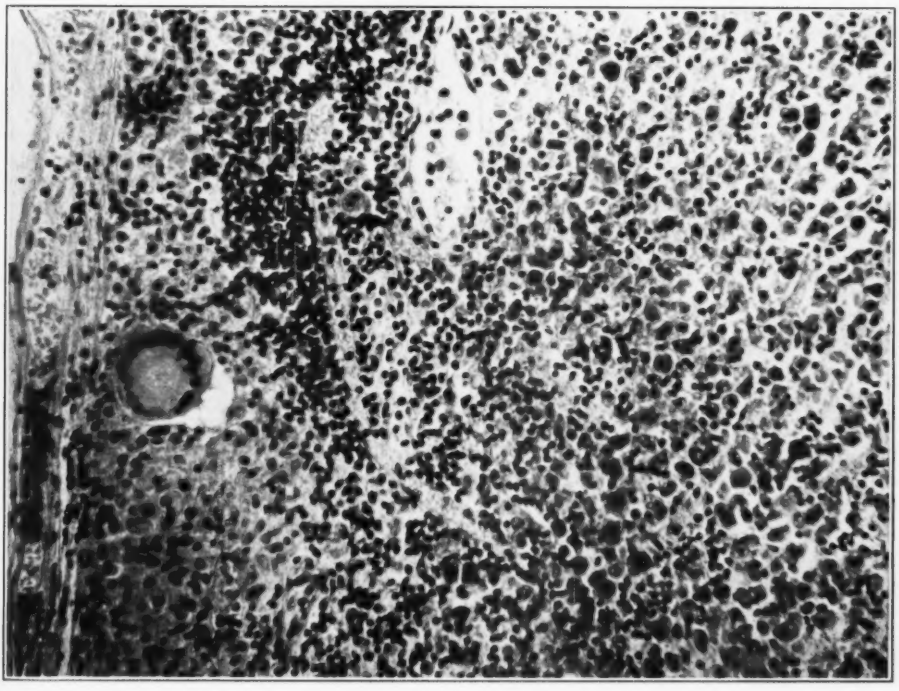

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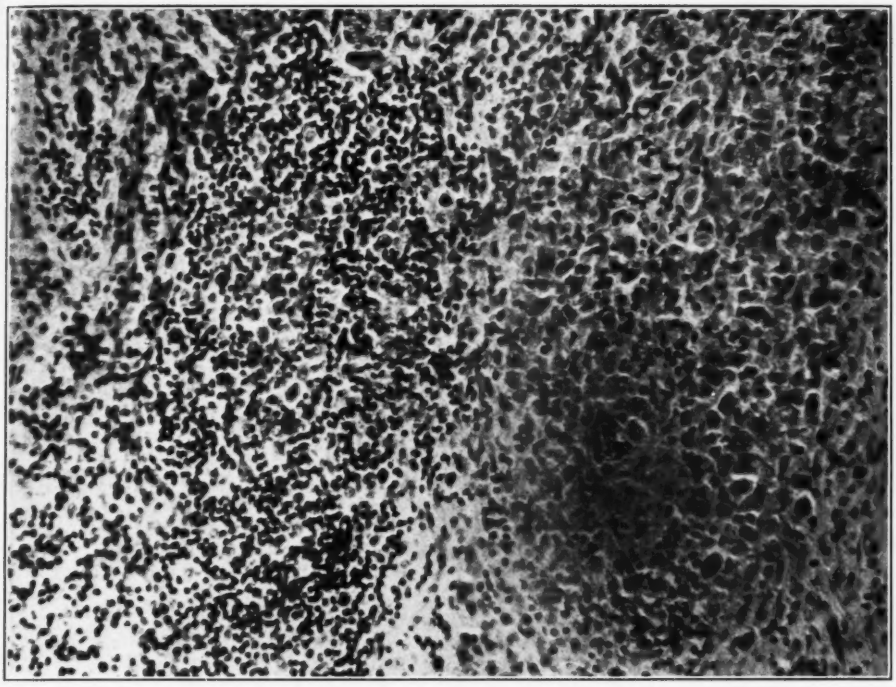
MacMahon and Parker Lymphoblastoma, Hodgkin's Disease, Tuberculosis

PLATE 78

FIG. 3. Liver. On the right is a nodule of Hodgkin's disease. On the left is a leukemic infiltration. The latter is being invaded by the cells of the former. × 250.

FIG. 4. Lymph node. An area of Hodgkin's disease. In the upper left corner is a tumor giant cell; below it is a multiple mitosis. At the right is another multiple mitosis. The majority of the cells shown are of the same type with irregular nuclei and prominent nucleoli. There are also some small lymphocytes scattered among these Hodgkin's tumor cells. × 500.



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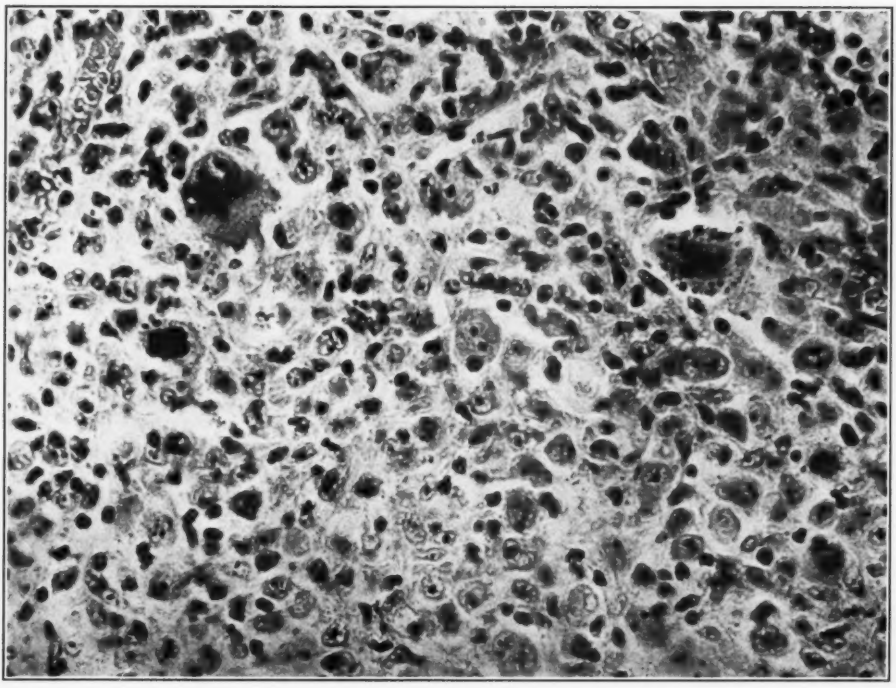

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MacMahon and Parker Lymphoblastoma, Hodgkin's Disease, Tuberculosis